

**RELATIONSHIP BETWEEN CHILDHOOD TRAUMA, NEUROPSYCHOLOGICAL
DEFICITS, NEURAL CIRCUITRY, AND ANXIETY PRONENESS IN HIGH-
ANXIETY PRONE AND LOW-ANXIETY PRONE ADOLESCENTS**

by

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Health Sciences at Stellenbosch University



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hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author
and are not necessarily to be attributed to the NRF.

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December 2017

DECLARATION

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This dissertation includes 3 original papers published in peer-reviewed journals or books and 3 unpublished publications. The development and writing of the papers (published and unpublished) were the principal responsibility of myself and, for each of the cases where this is not the case, a declaration is included in the dissertation indicating the nature and extent of the contributions of co-authors.

Lindi Martin

Date: December 2017

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SUMMARY

Anxiety disorders, which commonly have their onset during critical developmental periods of childhood, adolescence and early adulthood, are associated with high rates of comorbidity, chronicity, and impairment. A number of risk factors, notably anxiety-related temperamental traits, and environmental and genetic influences, have been implicated in the aetiology and maintenance of anxiety disorders.

Research to date, predominantly conducted in developed countries among Caucasian samples, has repeatedly shown that anxiety prone youth, characterized by elevated levels of self-reported anxiety-related temperamental traits [e.g., anxiety sensitivity and trait anxiety, together referred to as anxiety proneness (AP)] and/or youth with childhood maltreatment (CM) histories, manifest with deficits in a number of key neuropsychological domains, and in the processing of emotionally salient material. The present study investigated the effects of low and high levels of AP and CM on neuropsychological performance and emotion processing in a representative sample of predominantly non-Caucasian adolescents recruited from secondary schools in Cape Town, South Africa. In addition, the interactive effect of the BDNF *Val66Met* polymorphism and CM on susceptibility to AP in a subsample of mixed race adolescents was assessed.

The present study comprised a two-tier study in a non-clinical sample of adolescents. The 1st tier constituted a cross-sectional survey and utilized a stratified, two-stage cluster sampling design. The 2nd tier comprised a cross-sectional study in which participants were closely matched on age, ethnicity, gender and educational status. In the 2nd tier, participants underwent neuropsychiatric and neuropsychological assessments, and functional neuroimaging. Adolescents were categorized into four groups, based on self-reported levels of AP and CM, namely low AP and low CM, low AP and high CM, high AP and low CM, and high AP and high CM.

Evidence for the unique effects of AP and CM on verbal working memory were found. The interaction of AP with CM was associated with deficits in cognitive flexibility, processing speed, verbal fluency and IQ. In terms of emotion processing, neither AP nor CM had any significant main or combined effects on neural responses to negative or positive images, relative to neutral images, in the amygdala, hippocampus, or insula. There were no significant group differences in neural responses in the aforementioned regions. A trend for greater

activation in response to negative and positive images in the right amygdala was evident in anxiety prone adolescents, relative to those adolescents with low levels of AP. Lastly, a trend toward statistical significance in terms of an interaction effect of the BDNF *Met66* allele (relative to *Val66* homozygotes) and CM on AP was observed.

Our findings of the impact of AP and CM on various functional parameters, underscores the importance of screening adolescents for AP and CM and suggests the need for early intervention in youth focused on reducing levels of AP, reducing and preventing CM, and improving neuropsychological skills.

OPSOMMING

Angsversteurings, wat algemeen gedurende kritieke ontwikkelingsperiodes van kinderjare, adolessensie en vroeë volwassenheid begin, gaan met hoë vlakke van komorbiditeit, kronisiteit, en inkorting gepaard. 'n Aantal risikofaktore, veral angswerwante temperamentele eienskappe, en omgewings- en genetiese invloede, is by die etiologie en instandhouding van angsversteurings betrokke.

Navorsing tot op hede, hoofsaaklik uitgevoer in ontwikkelde lande onder Blanke steekproewe, het herhaaldelik getoon dat jeug wat geneig is tot ang, gekenmerk word deur verhoogde vlakke van self-gerapporteerde angswerwante temperamentele eienskappe [bv. ang-sensitiwiteit en eienskap-gebaseerde ang, gesamentlik verwys na ang-geneigdheid (AG)] en/of jeug met 'n geskiedenis van mishandeling in die kinderjare (KM), manifesteer met 'n tekort in 'n aantal belangrike kern neurosielkundige domeine, en in die prosessering van emosioneel opvallende materiaal. Die huidige studie ondersoek die gevolge van lae en hoë vlakke van AG en KM op neurosielkundige prestasie en emosionele prosessering in 'n verteenwoordigende steekproef, wat grotendeels uit nie-Blanke adolessente, wat gewerf is uit sekondêre skole in Kaapstad, Suid-Afrika, bestaan het. Addisioneel tot bogenoemde, was die interaktiewe effek van die BDNF *Val66Met* polimorfisme en KM op vatbaarheid tot AG in 'n steekproef van gemengde ras adolessente, geassesseer.

Die huidige studie het bestaan uit 'n twee-vlak studie in 'n nie-kliniese steekproef van adolessente. Die 1ste vlak is saamgestel uit 'n deursnit-opname wat gebruik gemaak het van 'n gestratifiseerde, twee-fase bundelsteekproef ontwerp. Die 2de vlak het bestaan uit 'n deursnee-studie waarin deelnemers gekoppel was op grond van ouderdom, etnisiteit, geslag en opvoedkundige status. Deelnemers het in die 2de vlak neuropsigiatriese en neurosielkundige assesserings ondergaan, asook funksionele breinbeelding. Adolessente is verdeel in vier groepe, gebaseer op self-gerapporteerde vlakke van AG en KM, naamlik lae AG en lae KM, lae AG en hoë KM, hoë AG en lae KM, en 'n hoë AG en hoë KM.

Bewyse vir die unieke effekte van AG en KM op verbale werkende geheue is gevind. Die interaksie van AG met KM is geassosieer met tekorte aan kognitiewe buigsaamheid, verwerkingspoed, verbale vlotheid en IK. In terme van emosionele prosessering, is daar bevind dat beide AG en KM nie 'n beduidende hoof of gekombineerde effek op neurale reaksies op negatiewe of positiewe beelde, relatief tot neutrale beelde, in die amigdala, hippocampus, of

insula, gehad het nie. Daar was geen beduidende groepsverskille in neurale reaksies in die bogenoemde dele nie. 'n Tendens vir meer aktivering in reaksie op negatiewe en positiewe beelde in die regte amigdala is gevind in AG adolessente, in vergelyking met adolessente met lae vlakke van AG. Laastens, 'n neiging tot statistiese beduidenheid, in terme van 'n interaksie effek van die BDNF *Met66* alleel (relatief tot *Val66* homosigote) en KM op AG, is waargeneem.

Ons bevindinge van die impak van AG en KM op verskeie funksionele parameters, beklemtoon die belangrikheid om adolessente te assesser vir AG en KM, en dui op die behoefte aan vroeë intervensie in jeug, gefokus op die vermindering van AG vlakke, vermindering en voorkoming van KM, en die verbetering van neurosielkundige vaardighede.

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- (2) **Martin, L.**, du Plessis, S., Kidd, M., Vink, M., & Seedat, S. Emotion processing in a non-clinical sample of older adolescents with high and low levels of both anxiety proneness and childhood maltreatment: An exploratory neuroimaging study. (**Manuscript in preparation**).
- (3) **Martin, L.**, Hemmings, S.M.J., Kidd, M., & Seedat, S. (2016). Gene-by-environment interaction of BDNF *Val66Met* polymorphism and childhood maltreatment on anxiety proneness in a mixed race adolescent sample. (**Manuscript in preparation**).
- (4) **Martin, L.**, Kidd, M., & Seedat, S. (2016). Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African sample. *Frontiers in Psychology*, 6, 1-10.
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- (6) **Martin, L.**, Viljoen, M., Kidd, M., & Seedat, S. (2014). Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth? *Journal of Affective Disorders*, 168, 5-12.

LIST OF ABBREVIATIONS

A-COPE	- Adolescent Coping Orientation for Problem Experiences
ADI	- Adolescent Drinking Inventory
AP	- Anxiety prone/anxiety proneness
AS	- Anxiety sensitivity
AUDIT	- Alcohol Use Disorders Identification Test
BDNF	- Brain-Derived Neurotrophic Factor
CASI	- Childhood Anxiety Sensitivity Index
CDI	- Children's Depression Inventory
CD-RISC	- Connor-Davidson Resilience Scale
CES-DC	- Centre for Epidemiological Depression Scale for Children
CM	- Childhood maltreatment
COWAT	- Controlled Oral Word Association Test
CTQ	- Childhood Trauma Questionnaire
DSM-IV	- Diagnostic and Statistical Manual of Mental Disorders 4 th edition
DUDIT	- Drug Use Disorders Identification Test
EHI	- Edinburgh handedness Inventory
fMRI	- Functional Magnetic Resonance Imaging
GPT	- Grooved Pegboard Test
HPA	- Hypothalamic-Pituitary-Adrenal axis
IAPS	- International Affective Picture System
MASC	- Multidimensional Anxiety Scale for Children
MINI-KID	- Mini-International Neuropsychiatric Interview – Kid for Children and Adolescents
MMSE	- Mini-Mental State Examination
RAVLT	- Rey Auditory Verbal Learning Test
ROCF	- Rey-Osterreith Complex Figure Test
SSAIS-R	- Senior South African Individual Scale – Revised
SSAT	- Stop-Signal Anticipation Task
STAI-S	- State-Trait Anxiety Inventory – State
STAI-T	- State-Trait Anxiety Inventory – Trait
TA	- Trait anxiety
TMT-A	- Trail Making Test Part A

- TMT-B** - Trail Making Test Part B
- TOL** - Tower Of London
- WASI** - Wechsler Abbreviated Scale of Intelligence
- WMS-R** - Wechsler Memory Scale – Revised
- 5-HTTLPR** - Serotonin transporter gene

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CHAPTER 1

INTRODUCTION

This chapter provides the rationale and significance for the study, as well as the study objectives and associated hypotheses. Thereafter, an overview of each of the chapters presented in this dissertation is provided.

1.1 Introduction and significance

The prevalence of DSM-IV (American Psychiatric Association, 1994) anxiety disorders is high in youth, with cumulative lifetime rates ranging up to 30% (Asselmann & Beesdo-Baum, 2015). A recent meta-analysis showed that over 10% of children and adolescents met criteria for a DSM-IV anxiety disorder in either middle childhood or adolescence (Costello, Egger, Copeland, Erkanli, & Angold, 2011), with over 20% of individuals meeting criteria by early adulthood (Copeland et al., 2014). In addition to these high rates, anxiety disorders commonly have their onset during the critical developmental periods of childhood, adolescence and early adulthood (Asselmann & Beesdo-Baum, 2015; Kessler et al., 2005; Merikangas, Nakamura, & Kessler, 2009; Pine, Cohen, Gurley, Brook, & Ma, 1998) and are frequently comorbid (Merikangas et al., 2009), persistent, chronic conditions (Kessler et al., 2012). Childhood and adolescent anxiety disorders are commonly associated with significant impairment in academic, social and family functioning, as well as adverse functioning and disability in early adulthood (Asselmann & Beesdo-Baum, 2015; Essau, Lewinsohn, Olaya, & Seeley, 2014; Langley, Bergman, McCracken, & Piacentini, 2004).

The development and persistence of anxiety disorders are associated with a number of well-documented factors that have been implicated in the aetiology of child and adolescent anxiety disorders (Murray, Creswell, & Cooper, 2009). These include genetic influences (Domschke & Reif, 2012; Norrholm & Ressler, 2009), cognitive or information processing styles (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Marques, Pereira, Barros, & Muris, 2013; Watts & Weems, 2006), environmental influences such as childhood adversity (Benjet, Borges, & Medina-Mora, 2010), and learning factors such as social modeling (Fisak & Grills-Tauchel, 2007). These vulnerability factors commonly influence or

interconnect with one another (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010) to produce potentially maladaptive outcomes.

Anxiety proneness (AP), characterized by elevated levels of self-reported anxiety-related temperamental traits (Stein, Simmons, Feinstein, & Paulus, 2007), is reflected in traits such as anxiety sensitivity (AS) (Reiss, Peterson, Gursky, & McNally, 1986) and trait anxiety (TA) (Eysenck, 1992), both developmentally stable risk factors for anxiety disorder (Garcia et al., 2013; Zavos, Gregory, & Eley, 2012; Zavos, Rijdsdijk, & Eley, 2012). Individuals with childhood maltreatment (CM) histories have also been shown to be at greater risk of developing anxiety disorders and associated psychopathology (Collishaw et al., 2007; Kessler et al., 2010). High anxiety prone (AP) adolescents with CM histories are particularly vulnerable to the development of a wide range of psychiatric disorders and in light of this, further investigation is warranted.

Neuropsychological deficits have been reported in individuals with elevated levels of anxiety-related temperamental traits as well as in those with CM histories (Barnard, Broman-Fulks, Michael, Webb, & Zawilinski, 2011; Eysenck, Derakshan, Santos, & Calvo, 2007; Irigaray et al., 2013; MacLeod & Donnellan, 1993; Owens, Stevenson, Norgate, & Hadwin, 2008; Vasilevski & Tucker, 2016). In addition, functional neuroimaging (fMRI) studies have shown that both AP individuals and individuals with CM histories demonstrate deficits in emotion processing. Such deficits are reflected in increased activity in the amygdala and associated brain regions in response to processing facial expressions of emotion, particularly threat-related images or facial expressions depicting fear and anger (Dannlowski et al., 2012; Stein et al., 2007; van Harmelen et al., 2013).

In addition to the above, certain genetic polymorphisms, for example, of the serotonin transporter gene (gene, *SLC6A4*; variant, 5-HTTLPR) and brain-derived neurotrophic factor (BDNF *Val66Met*), have been shown to be associated with anxiety-related temperamental traits (Gonda et al., 2009; Sen et al., 2003; Stein, Schork, & Gelernter, 2008) and anxiety disorders (Mushtaq, Shoib, Shah, & Mushtaq, 2014; Tocchetto et al., 2011). There is also evidence for a moderating role of genetic polymorphisms (e.g. BDNF *Val66Met*) in the relationship between life stress, including CM, and subsequent risk for psychopathology in youth and adults (Carver, Johnson, Joormann, Lemoult, & Cuccaro, 2011; Chen, Li, & McGue, 2013; Gutiérrez et al., 2015; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014).

Given the above, adolescents with increased levels of anxiety-related temperamental traits and histories of CM may be particularly vulnerable to psychiatric and neuropsychological impairment as a result of additive or interactional effects of AP and CM, in addition to genetic vulnerability. The literature on the impact of varying levels of AP and CM on neurocognitive functioning (i.e. neuropsychological test performance and emotion processing) is limited, as is the role of genetic variants in the development of anxiety-related traits in the context of childhood adversity. More research is needed to provide a clearer understanding of the mechanisms underlying the adverse effects of AP and CM in adolescents, particularly older adolescents, defined by the World Health Organization as those aged between 15 and 19 years (Patton et al., 2016). The majority of studies that have assessed the aforementioned have been conducted in developed, high income, high resource countries, and predominantly in Caucasian samples. In contrast, South Africa is a developing, low-middle income, low resource country, characterized by high levels of poverty, unemployment and violence, which constitute risk factors for poor child and adolescent mental health (Patel, Flisher, Nikapota, & Malhotra, 2008). A significant portion of children and adolescents in South Africa are exposed to such negative factors. Mental health resources in South Africa, including the number of mental health professionals, are markedly lower than in higher income countries, suggesting an inability to provide appropriate evidence-based mental health care to vulnerable populations (Bruckner et al., 2011), potentially resulting in chronicity of psychological conditions and increased costs of care (Patel, 2007). The exposure to adverse conditions, such as those mentioned above, including the maltreatment of children and adolescents, together with sub-optimal mental health care resources, place vulnerable children and adolescents in South Africa at increased risk for the development and maintenance of psychopathology. Investigating adolescents with AP and early developmental trauma provides a unique opportunity to examine the potential unique and combined effects of these vulnerability factors on neuropsychological functioning and emotion processing in healthy adolescents, as well as the contribution of genetic influences on susceptibility to anxiety, in the context of CM.

1.2 Objectives

1.2.1 Primary objectives

- (i) to assess the predictive ability of CM and AP, as well as the combined effect of CM and AP, on neuropsychological performance, in healthy older adolescents with high and low levels of CM and high and low levels of AP,
- (ii) to compare brain functional activity among healthy older adolescents with high and low levels of CM and high and low levels of AP in bilateral amygdala, bilateral hippocampus, and bilateral insula, and
- (iii) to investigate the interaction of gene variants (polymorphisms) in the serotonin transporter gene (5-HTTLPR) and Brain Derived Neurotrophic Factor (BDNF) genes in mediating AP, in the context of CM.

1.3 Study hypotheses

- (i) CM and AP would have main and interactive effects on neuropsychological performance in older adolescents with high levels of CM and high levels of AP,
- (ii) Older adolescents with high levels of CM and high levels of AP would demonstrate significantly more pronounced neural deficits compared with older adolescents with comparable levels of CM who have low levels of AP, and
- (iii) Genetic polymorphisms of the 5-HTTLPR and BDNF genes would interact with CM in mediating AP.

1.4 Overview of chapters

Chapter 2: This chapter provides an overview of the epidemiology of anxiety disorders and CM, as well as aetiological factors associated with anxiety disorders. Furthermore, in this chapter, focus is placed on CM and the concept of AP (i.e. elevated levels of AS and TA) and the neuropsychological and emotion processing deficits associated with each. In addition, genetic polymorphisms in specific candidate genes (i.e. serotonin transporter and BDNF) associated with anxiety and CM are discussed.

The reader is referred to a published manuscript based on this study's data [Hemmings, S.M.J, **Martin, L.I.**, van der Merwe, L., Benecke, R., Domschke, K., & Seedat, S. (2016). Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents. *The World Journal of Biological Psychiatry*, 17(1), 66-75].

Chapter 3: This chapter outlines the methods utilized in the present study, including the study design, sampling, participant selection, participant categorization, data collection instruments, neuroimaging parameters, genetic sampling and analysis, and data analyses procedures.

The reader is referred to two published manuscripts based on this study's data. The first manuscript is based on data collected in the first tier of the study. It assesses the predictive potential of CM on AS and provides a description of the sample, procedure, data collection instruments, and the first tier's outcomes [**Martin, L.**, Viljoen, M., Kidd, M., & Seedat, S. (2014). Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth? *Journal of Affective Disorders*, 168, 5-12].

The second manuscript is based on data collected in the first tier of the study and addresses the applicability of the Childhood Anxiety Sensitivity Index (CASI) as assessed by exploratory and confirmatory factor analysis [**Martin, L.**, Kidd, M., & Seedat, S. (2016). Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African sample. *Frontiers in Psychology*, 6, 1-10].

Chapter 4: This chapter, which addresses the first aim of the study, is titled 'The effects of childhood maltreatment and anxiety proneness on neuropsychological performance in non-clinical older adolescents'. This has been submitted as a research paper to Child Abuse and Neglect and is currently under review.

Chapter 5: This chapter, which addresses the second aim of the study, is titled 'Emotion processing in a non-clinical sample of older adolescents with high and low levels of both anxiety proneness and childhood maltreatment: An exploratory neuroimaging study'. This chapter has been prepared as a research paper and will be submitted to a relevant journal.

Chapter 6: This chapter, which addresses the final aim of the study, is titled 'Gene-by-environment interaction of BDNF *val66met* polymorphism and childhood maltreatment on

anxiety proneness in a mixed race adolescent sample'. This chapter has been prepared as a research paper and will be submitted to a relevant journal.

Chapter 7: This chapter provides an overview of key study findings, contributions to knowledge gaps, and study limitations.

Chapter 8: This chapter provides a comprehensive conclusion, implications for practice, and recommendations for future research.

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CHAPTER 2

BACKGROUND

2.1 Introduction

The following chapter provides an overview of the epidemiology and aetiology of anxiety disorders. In addition, key literature pertaining to childhood maltreatment (CM) is presented, including prevalence, associated psychopathology, effects on the developing brain, neuropsychological functioning, and brain functional deficits associated with emotion processing. Anxiety-related temperamental traits, namely, anxiety sensitivity (AS) and trait anxiety (TA), are discussed in terms of their definitions, associations with psychopathology, neuropsychological performance, and brain functional deficits associated with emotion processing. Finally, the heritability of AS and TA are discussed, and literature relating to genetic polymorphisms (i.e. of the serotonin transporter gene and the brain-derived neurotrophic factor), associated with CM and anxiety proneness (AP), is presented.

2.2 Epidemiology of anxiety disorders

Epidemiological studies have determined that anxiety disorders are among the most prevalent category of psychiatric disorders among adults, adolescents and children both globally (Baxter, Scott, Vos, & Whiteford, 2013, Cartwright-Hatton, McNicol, & Doubleday, 2006; Kessler et al., 2012; Kessler, Chiu, Demler, & Walters, 2009; Kessler, Berglund, et al., 2009; Merikangas et al., 2010) and locally (Cortina, Sodha, Fazel, & Ramchandani, 2012; Stein et al., 2008; Williams et al., 2008).

In terms of the prevalence of anxiety disorders in children and adolescents in South Africa, no large-scale studies in nationally representative samples of youths have been conducted. There is, however, evidence to suggest that the prevalence of anxiety disorders in children and adolescents in South Africa is high. For example, based on a systematic review of both local and international studies, Kleintjes and colleagues (2006) provided annual prevalence estimates of psychiatric disorders in children, adolescents and adults in the Western Cape. Findings indicated an overall estimated prevalence of 17% in children and adolescents, with anxiety disorders being the most prevalent group of disorders in youths [i.e. generalized anxiety

disorder (11%), posttraumatic stress disorders (8%)] (Kleintjes et al., 2006). Adjusted for comorbidity, a rate of 2.75% and 2% was estimated for these two disorders, respectively (Kleintjes et al., 2006). In addition, a few community-based and school-based studies in the Western Cape Province of South Africa have reported that a large portion of children and adolescents are at risk for developing mental health problems, and that the 6-month period prevalence for mental disorders in youth is high (Pluddemann et al., 2014; Robertson, Ensink, Parry, & Chalton, 1999). Pluddemann and colleagues (2014) surveyed over 20 000 students aged 12 to 22 years, from grades 8 to 10, from 227 secondary schools in the Western Cape Province and determined that overall, 14.9% of students were at high risk for developing mental health problems (41.4% were categorized as ‘medium risk’ and 43.7% as ‘low risk’). Furthermore, significantly more female students than male students were categorized as being at ‘high risk’ (Pluddemann et al., 2014). Robertson and colleagues (1999) determined that the 6-month period prevalence for mental disorders (i.e. either one or more) with impairment, in a community sample of 500 children and adolescents aged 6 to 16 years from Khayelitsha, an informal settlement area in Cape Town, was 15.2%. Prevalence rates, with impairment, for anxiety and depressive disorders were 2.8% and 4.4%, respectively. Increased rates of mental disorders were associated with residing in unserviced areas, scarcity of food, previous hospitalization, and previous physical problems or serious illness (Robertson et al., 1999). In addition, a systematic review of the prevalence of general psychopathology of children and adolescents in sub-Saharan Africa, including South Africa, identified risk factors for the development of psychopathology, which included, amongst others, disruption of the family, exposure to stressful life events, and poverty-related factors (Cortina et al., 2012).

Anxiety disorders commonly develop during childhood or adolescence, which is earlier than the median age of onset of a number of other psychiatric disorders, such as substance use disorders and mood disorders (Kessler et al., 2009). Anxiety disorders are frequently comorbid (Leyfer, Gallo, Cooper-Vince, & Pincus, 2013; Merikangas, Nakamura, & Kessler, 2009), highly persistent, chronic conditions (Asselmann & Beesdo-Baum, 2015; Beesdo-Baum & Knappe, 2012; Kessler et al., 2012). Childhood and adolescent anxiety disorders are commonly associated with substantial disability and impairment in academic, social and family functioning (Langley, Bergman, McCracken, & Piacentini, 2004).

2.3 Aetiological factors associated with anxiety disorders

It has been suggested that anxiety in children and adolescents stems from a complex interplay of multiple causal mechanisms associated with the individual, as well as negative influences in the individual's environment (Dabkowska & Dabkowska-Mika, 2015; Keeley & Storch, 2009; Weems & Stickle, 2005). These mechanisms are thought to act in a transactional or multiplicative manner rather than independently or additively (Weems & Stickle, 2005). Biological risk factors include, amongst others, genetic influences (Domschke & Reif, 2012; Norrholm & Ressler, 2009), anxiety-related temperamental traits (Weems & Stickle, 2005), and cognitive or information processing biases (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Marques, Pereira, Barros, & Muris, 2013; Watts & Weems, 2006). Environmental influences include early life adversity, such as CM (Benjet, Borges, & Medina-Mora, 2010; De Bellis & Thomas, 2003; Lewis, Byrd, & Ollendick, 2012; McCullough, Miller, & Johnson, 2010; Young & Dietrich, 2015). Furthermore, learning factors, including social modelling and information transfer, are also associated with anxiety in youth (Fisak & Grills-Tauchel, 2007).

Genetic epidemiological studies have provided evidence for the association between genetic determinants and anxiety (Arnold, Zai, & Richter, 2004; Hettema, Neale, & Kendler, 2001; Maron, Hettema, & Shlik, 2008). Considerable familial aggregation has been determined for phobias, panic disorder, generalized anxiety disorder and obsessive-compulsive disorder, with odds ratios ranging from 4.0 to 6.0 (Hettema et al., 2001), indicative of a moderate level of familial aggregation (Maron et al., 2008). Furthermore, moderate heritability estimates, ranging from 30% to 50%, depending on both the disorder and sample assessed, have been demonstrated (Maron et al., 2008). Moreover, the risk of a child developing an anxiety disorder has been suggested to be twice as high if a parent has an anxiety disorder, and five times higher if both parents have anxiety disorders (Li, Sundquist, & Sundquist, 2008). In terms of anxiety-related temperamental traits or phenotypes, such as AS, moderate heritability estimates (37% to 48%) have been determined in samples of youths and adults (Eley, Gregory, Clark, & Ehlers, 2007; Stein, Jang, & Livesley, 1999; Zavos, Rijdsdijk, Gregory, & Eley, 2010). Similarly, in terms of TA, heritability has been estimated to be moderate, around 45%, in children and adolescents (Legrand, McGue, & Iacono, 1999).

In addition to genetic influences, it has been suggested that child temperament is associated with the manifestation and maintenance of both emotional and behavioural disorders in youth (Muris & Ollendick, 2005). Temperamental traits that have been widely studied and found to be associated with anxiety disorder symptoms in youth include, amongst others, behavioural inhibition (Muris, Meesters, Bouwman, & Notermans, 2014), neuroticism (Hong, 2010; Paulus, Vanwoerden, Norton, & Sharp, 2016), TA, and AS (McLaughlin, Stewart, & Taylor, 2007; Muris, Schmidt, Merckelbach, & Schouten, 2001; Viana, Gratz, & Bierman, 2013). Elevated levels of these traits, such as, TA and AS, are evident in youth with anxiety disorders relative to non-anxious youth (Gauthier, Chevette, Bouvier, & Godbout, 2009; Noël & Francis, 2011).

Information processing biases play an important role in the maintenance of anxiety disorders (Craske & Pontillo, 2001; Micco, 2015) and include attentional biases towards fear or threat-related information, interpretation biases and memory biases (Watts & Weems, 2006). Selective attention to threat involves focused attention towards potentially threatening or threatening stimuli in the presence of non-threatening or neutral stimuli (Watts & Weems, 2006); interpretation bias refers to the selection of either threatening or negative interpretations of information that is objectively neutral or ambiguous (Micco, 2015); and memory bias refers to the tendency towards the recall of threatening or negative information (Watts & Weems, 2006). It is well established that such cognitive biases are evident in clinically anxious youth and adults (Bar-Haim et al., 2007; Dalglish et al., 2003; Moradi, Taghavi, Neshat-Doost, Yule, & Dalglish, 2000; Muris & Field, 2008; Rozenman, Amir, & Weersing, 2014), however, mixed results have been reported, with clinically anxious youths, for example, displaying age-specific attentional bias either towards or away from threat (Carmona et al., 2015).

The transmission of anxiety within families has been suggested, indicative of bi-directional influences (Fisak & Grills-Tauechel, 2007), evidenced by the high prevalence of anxiety disorders in children whose parents have an anxiety disorder (i.e. up to 80%), and by the high prevalence of anxiety disorders in parents with an anxious child or children (i.e. 54% to 78%) (Ginsburg & Schlossberg, 2002; Martin, Cabrol, Bouvard, Lepine, & Mouren-Siméoni, 1999), demonstrating the likely role of both genetic and environmental influences on child anxiety disorders (Drake & Ginsburg, 2011). Learning experiences associated with youth anxiety include modelling, which involves the observation of others' anxiety by the child; information transfer/verbal instruction, which involves communicating information to the child with regard

to the threatening or negative properties of the environment; and parental reinforcement or encouragement of anxious and/or avoidant symptoms and behaviour (Fisak & Grills-Taquechel, 2007; Murray, Creswell, & Cooper, 2009). In children with various psychiatric diagnoses including anxiety, behaviour and depressive disorders, it was found that the children of mothers who often expressed their fears in the child's presence, had the highest total fear scores, and that the relationship between fearfulness of the mother and fearfulness of the child was mediated by modelling (Muris, Steerneman, Merckelbach, & Meesters, 1996).

Family and parenting factors such as attachment styles and parental rearing behaviours have been found to make an important contribution to the development of anxiety disorders in youth (Ginsburg, Siqueland, Masia-Warner, & Hedtke, 2004; Wei & Kendall, 2014; Whittle et al., 2016). Maternal insecure attachment relationship, maternal rejection and overprotection, have been found to be associated with anxiety disorder symptoms in normal children and adolescents (Breinholst, Esbjørn, & Reinholdt-Dunne, 2014), as have insecure attachment and the parental rearing styles of 'control/over-control', 'anxious rearing', and 'rejection' (Muris et al., 2006; van Brakel, Muris, Bögels, & Thomassen, 2006). Cultural differences in parenting practices and their associations with child anxiety are important to consider. For example, in healthy school attending children and adolescents, Black and mixed race youths had significantly higher anxiety scores than white youths and also viewed the rearing behaviours of their parents as more anxious, more overprotective, and more rejective, and less emotionally warm than did white youths, despite the comparable association across groups between parental control and child anxiety (Muris et al., 2006; Wei & Kendall, 2014). Such differences have been explained in terms of potentially less favourable living conditions (e.g. poverty and violence) experienced by non-Caucasian youths, associated with increased stress and threat and consequent rearing behaviours, such as parental overprotection (Muris et al., 2006). Notably, it has been shown that the relationship between stressful life events and anxiety severity in children of parents with anxiety disorders, is mediated by both child-reported 'anxious rearing' and parent-reported 'parent-child dysfunctional interaction' (Platt, Williams, & Ginsburg, 2015).

The experience of early childhood adversity or stressful or negative life events has been shown to be a risk factor for the development of anxiety disorders in both adults and youth. Epidemiological surveys conducted in 21 countries that included over 50 000 adults, determined that early life adversities are associated with first onset of all classes of disorders, with the strongest predictors of DSM-IV/CIDI (American Psychiatric Association, 1994;

World Health Organization, 1993) disorders being those childhood adversities associated with maladaptive family functioning (i.e. parental psychopathology and child maltreatment) (Kessler et al., 2010). Similarly, in a longitudinal study in a birth cohort of 816 adolescents, it was reported that the total number of early life adversities was significantly associated with the later development of anxiety disorders (Phillips, Hammen, Brennan, Najman, & Bor, 2005). Adversities associated with later anxiety in the aforementioned study, controlling for gender and maternal depression and anxiety, included maternal prenatal stress and multiple maternal partner changes (Phillips et al., 2005). It was also noted that early adversity factors remained significantly associated with youth anxiety even when current family stressors at age 15 years were controlled (Phillips et al., 2005). Furthermore, other types of early adversities associated with anxiety disorders in youth include, harsh discipline, dangerous neighbourhood, parental drug use, step-parent (Shanahan, Copeland, Costello, & Angold, 2008), family violence and CM (McLaughlin et al., 2012).

2.4 Childhood maltreatment

2.4.1 Definitions of childhood maltreatment abuse and neglect categories

As the current study employed the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003) to assess retrospectively levels of abuse and neglect experienced in childhood (i.e. up to 12 years of age), the definitions of abuse and neglect types, according to Bernstein et al. (2003) will be provided. Bernstein and colleagues define sexual abuse as “sexual contact or conduct between a child younger than 18 years of age and an adult or older person.” Physical abuse is defined as “bodily assaults on a child by an adult or older person that posed a risk of or resulted in injury.” Emotional abuse is defined as “verbal assaults on a child’s sense of worth or well-being or any humiliating or demeaning behavior directed toward a child by an adult or older person.” Physical neglect is defined as “the failure of caretakers to provide for a child’s basic physical needs, including food, shelter, clothing, safety, and health care.” Emotional neglect is defined as “the failure of caretakers to meet children’s basic emotional and psychological needs, including love, belonging, nurturance, and support.”

2.4.2 Childhood trauma exposure and victimization

Previous studies have determined that the prevalence of trauma exposure and victimization in both children and adolescents globally and locally is both high and common (Cyr et al., 2013; Finkelhor, Ormrod, & Turner, 2009; Martin, Revington, & Seedat, 2013; Seedat, Nyamai, Njenga, Vythilingum, & Stein, 2004; Suliman et al., 2009). For example, in a population survey conducted in Canada in a large sample of children and adolescents, Cyr and colleagues (2013) found that 75.7% of youths were victimized during their lifetime and 61% experienced being victimized in the last year (Cyr et al., 2013). Overall lifetime victimizations have been found to correlate significantly with both trauma symptoms and other lifetime adversities (David Finkelhor et al., 2009). Some studies conducted in Southern Africa have similarly shown very high rates of trauma exposure in youth. Seedat and colleagues (2004) found that over 80% of school-attending youth reported lifetime exposure to at least one DSM-IV qualifying trauma, with the average number of trauma exposures being 2.49, ranging from 0-11 exposures. In the aforementioned study, the most frequently reported traumas were witnessing community violence, being robbed or mugged, and witnessing a family member being hurt or killed. In addition, it was determined that those participants that met criteria for posttraumatic stress disorder endorsed a higher number of traumas than those without the disorder (Seedat et al., 2004). A study conducted in school-attending adolescents in South Africa (Collings, Valjee, & Penning, 2013) determined that the median age of earliest exposure/awareness of exposure was 0 years to 6 years for exposure to poverty; 7 to 12 years for exposure to domestic violence, emotional abuse, neglect, loss and/or separation; and 13 to 18 years for sexual abuse, as well as exposure to direct and indirect community violence. Furthermore, the most frequently reported trauma experiences were witnessing community violence, domestic assault, indecent assault and community assault, witnessing family violence, emotional abuse and neglect (Collings et al., 2013). Childhood abuse and neglect types and general adverse childhood experiences commonly co-occur (Arata, Langhinrichsen-Rohling, Bowers, & O'Brien, 2007; Dong et al., 2004; Flynn, Cicchetti, & Rogosch, 2014; Kessler et al., 2010; McLaughlin et al., 2012), and prior victimization is associated with vulnerability to future victimization (Cuevas, Finkelhor, Clifford, Ormrod, & Turner, 2010; Finkelhor, Ormrod, & Turner, 2007). Onset of poly-victimization (i.e. high levels of victimizations across differing victimization types) in youth is associated with living in a dangerous community, living in a family where violence and conflict is common, living in a family characterized by multiple problems, and child behavioural and emotional problems (Finkelhor, 2009).

2.4.3 Prevalence of childhood maltreatment

CM frequently occurs across multiple developmental periods, with onset being predominantly during infancy, followed by young childhood and later childhood (Flynn et al., 2014). Infancy and young childhood are associated with lower rates of maltreatment, with rates increasing in older children and levelling off and remaining fairly stable across the periods of childhood and adolescence (Trickett, Negriff, Ji, & Peckins, 2011).

The reported prevalence of CM both globally and locally varies largely across studies due to differences in methodology, including maltreatment definitions, data collection procedures, the types of samples studied, the age used to define CM (Pereda, Guilera, Forns, & Gómez-Benito, 2009a), differing understandings of what CM constitutes (Pereda et al., 2009a), forms of CM assessed, cultural variation in understandings of CM, and societal norms that vary by culture and country (Richter & Dawes, 2008). Regardless of these discrepancies, rates of CM globally are high. Epidemiological surveys conducted in 21 countries (i.e. high-income, high-middle income, and low/lower-middle-income countries) in adult samples, determined the following rates of CM (i.e. prior to 18 years of age) in the total sample: 8.0% for physical abuse, 4.4% for neglect, 1.6% for sexual abuse, with 6.5% of the sample reporting exposure to family violence (Kessler et al., 2010). The rates of CM determined in participants from high-middle income countries in the aforementioned study, including South Africa, were as follows: 10.8% for reported physical abuse, 5.2% for neglect, 0.6% for sexual abuse, and 7.1% for exposure to family violence (Kessler et al., 2010). In terms of childhood neglect, a meta-analytic review of studies in adults determined rates of 16.3% and 18.4% for physical and emotional neglect, respectively (Stoltenborgh, Bakermans-Kranenburg, & Van Ijzendoorn, 2013). In terms of child sexual abuse, a meta-analysis of the global prevalence of child sexual abuse in community and student samples, determined a mean prevalence of 19.7% and 7.9% for females and males, respectively (Pereda, Guilera, Forns, & Gómez-Benito, 2009b). Notably, the highest prevalence of child sexual abuse determined in the previous analysis was evident in Africa (i.e. 34.4%), with South African studies reporting the highest rates for both women and men (Pereda et al., 2009b). Differing rates of child sexual abuse frequently reported between the genders are associated with a number of factors, including developmental stage of the individual (e.g. early adolescence vs. older or late adolescence), difficulties or fears associated with disclosure (e.g. males being viewed as victims or homosexuals, females not being believed or blamed) and the underreporting of child sexual abuse, particularly amongst males (Alaggia, 2005; Finkelhor,

Shattuck, Turner, & Hamby, 2014; Holmes, Offen, & Waller, 1997; Rumble et al., 2015). Substantially more female youth, relative to male youth, disclose their experiences of abuse (Ungar, Barter, McConnell, Tutty, & Fairholm, 2009), particularly sexual abuse (Hershkowitz, Horowitz, & Lamb, 2005). Commonly, children of both genders delay disclosure of sexual abuse until adulthood (McElvaney, 2015).

Importantly, the assessment of CM in adults is associated with an increased risk of recollection bias (Schulz et al., 2014), however, this risk is reduced in studies in youth (Barth et al., 2013). Similarly high rates of CM determined in adult samples have been reported in community and school samples of youth. For example, rates of CM in adolescents in the United States have been estimated as follows: 4.2% for physical abuse, 4.4% for sexual abuse, 5.9% for emotional abuse, 2.2% for neglect, and 8.4% for exposure to family violence (McLaughlin et al., 2012).

A number of studies conducted in South Africa have provided evidence for high rates of maltreatment among youth. Pieterse (2015) determined that a large portion of youth (i.e. Black, mixed race, and Caucasian) in Cape Town had experienced violence perpetrated against them during childhood, within their homes, by their parents. Overall CM rates determined were 20%, 19%, and 10% in mixed race youths, Black youths, and Caucasian youths, respectively (Pieterse, 2015). Madu (2001) determined substantially higher rates of CM in a sample of predominantly Black high school students, namely 70.7%, with high rates determined for contact sexual abuse (i.e. 54% overall, 53% for females and 60% for males), emotional abuse (i.e. 35.3%), physical abuse (i.e. 27%), psychological abuse (i.e. 14.4%), and ritualistic abuse (i.e. 10%) (Madu, 2001; Madu & Peltzer, 2001).

In addition to the studies reported above, another means of assessing the extent of child abuse in South Africa is to examine the number of crimes reported to the police that are committed annually against children (Richter & Dawes, 2008). Despite such rates having been found to be grossly underestimated (Finkelhor & Ormrod, 2001), the annual South African Police Service report for 2014/2015 indicated that of the total number of complaints reported, crimes against children comprised 4.5% of reported murders, 4.9% of reports of attempted murder, 4.6% of reports of grievous bodily harm, 6.2% of reports of common assault, and 36.2% of reports of sexual offences (*South African Police Service Annual Report 2014/2015*).

In terms of CM in South Africa, a number of risk factors have been determined, including, poverty and unemployment, South Africa being a violent society, patriarchy and gender violence, cultural beliefs and practices, parental attitudes and norms, family structure, alcohol and drug use, socialized obedience, and dependency (Richter & Dawes, 2008; UNICEF, 2012).

2.4.4 Childhood maltreatment and social, academic, and psychological outcomes

It is well established that the effects of CM are long-lasting or chronic (Hovens et al., 2010; Lindert et al., 2014) and are associated with a wide range of negative outcomes in youth. CM is frequently associated with:

- (1) physical health problems (Veldwijk, Proper, Hoeven-Mulder, & Bemelmans, 2012)
- (2) sleep disturbances (Brown et al., 2009)
- (3) psychological and social difficulties, such as increased feelings of loneliness (Brown et al., 2009), lower self-esteem (Turner, Finkelhor, & Ormrod, 2010), lower perceived competence, higher psychological distress (Sagy & Dotan, 2001), lower self-worth, lower maternal and peer relationship quality (Flynn et al., 2014), higher levels of peer rejection and peer acceptance (Kim & Cicchetti, 2010), poor coping behaviours (Flett, Druckman, Hewitt, & Wekerle, 2012), and lower levels of resilience (Collin-Vézina, Coleman, Milne, Sell, & Daigneault, 2011)
- (4) intellectual disability, academic underachievement (Jones, Trudinger, & Crawford, 2004), and higher probability of school dropout (Pieterse, 2015)
- (5) negative/risky behaviours, such as frequent substance use (Brown et al., 2009), suicide attempts and suicidal ideation (Miller, Esposito-Smythers, Weismore, & Renshaw, 2013), delinquency (Trickett et al., 2011), earlier transition to first sexual intercourse (Tenkorang & Obeng Gyimah, 2012) and other risky sexual behaviours (Brown et al., 2009).

CM constitutes a significant risk for the onset and development of psychopathology and psychiatric disorder(s) across all life stages (Benjet et al., 2010; Gilbert et al., 2009; Kessler et al., 2010). In youth, CM is significantly associated with trauma symptoms (Finkelhor et al., 2009) and is associated with increased internalizing and externalizing symptoms (Cecil, Viding, Barker, Guiney, & McCrory, 2014), mental and physical health problems, high-risk sexual behaviours, and exposure to violence as an adult (Barrios et al., 2015; Fry, McCoy, & Swales, 2012). Furthermore CM, rather than other adverse events experienced in childhood,

has been found to be associated with higher risk of psychopathology (e.g. anxiety and depressive disorders, and comorbid depression and anxiety) in adults (Hovens et al., 2010). Even after controlling for childhood family adversity, higher estimated rates of DSM-IV Axis-I disorders (i.e. suicidal behaviour, recurrent major depressive disorder, substance use disorders, and posttraumatic stress disorder) have been determined in adults with CM histories, compared with non-maltreated adults (Collishaw et al., 2007). Moreover, a history of CM is associated with earlier onset of clinical disorder, greater severity and persistence of disorder, increased comorbidity, increased risk for suicide, and less favourable treatment outcome (Alvarez et al., 2011; Leverich et al., 2002; Nanni, Uher, & Danese, 2012; Teicher & Samson, 2013).

2.4.5 Stress and the developing brain

A physiological response occurs when an individual perceives or detects a threat, and this response involves activation of the sympathetic nervous system and hypothalamic–pituitary–adrenal (HPA) axis (Lupien, McEwen, Gunnar, & Heim, 2009; Pechtel & Pizzagalli, 2011). The acute activation of the individual’s stress response systems is considered adaptive so as to ensure survival, yet, elevated or chronic stress may have adverse effects on brain development, and may impact mental wellbeing (Pechtel & Pizzagalli, 2011). Indeed, the dysregulation of major stress systems, evident in those with CM histories, is thought to contribute to adverse brain development and subsequent psychopathology (De Bellis & Zisk, 2014).

Brain maturation is influenced by interactions between genes, cell function and the environment (Andersen, 2003; Lenroot et al., 2009; Teicher, Tomoda, & Andersen, 2006). In terms of genetic influences, strong genetic effects earlier in development are evident on earlier developing brain regions (e.g. regions of primary sensory cortex and motor cortex), while later-developing brain regions (e.g. dorso-lateral prefrontal cortex, superior parietal cortex, and temporal cortex), associated with more complex cognitive functions, such as language and executive functioning, are more affected by genetic influences with increasing age or maturation (Lenroot et al., 2009; Pechtel & Pizzagalli, 2011). The impact of early life adversity or stress on brain development may thus either be enhanced or moderated, depending on the timing and strength of genetic influences on particular brain regions (Pechtel & Pizzagalli, 2011).

Environmental influences such as adverse childhood experiences and early life stress, including CM, have profound and potentially long lasting neural effects on the developing brain. These effects are particularly evident on the HPA axis, and are reflected in structural and functional disturbances in emotion and stress-regulating structures (Anda et al., 2006; Rinne-Albers, van der Wee, Lamers-Winkelmann, & Vermeiren, 2013; Teicher et al., 2003), as well as those involved in higher-order, complex cognitive functions (Pechtel & Pizzagalli, 2011; Whittle et al., 2016). Such neurobiological disturbances potentially underlie the increased vulnerability to psychopathology in youth and adults exposed to early life stress (De Bellis & Zisk, 2014; Heim & Nemeroff, 2001). The effects of adverse environmental influences, such as early life adversity or early life stress, on important brain regions and functions are largely dependent on the age of onset of adversity, the type of adversity experienced, and the frequency of adverse experiences (Andersen, 2003; De Bellis & Zisk, 2014; Pechtel & Pizzagalli, 2011; Teicher et al., 2006). For example, in healthy young adults, associations between childhood sexual abuse and regional brain size during particular developmental stages, has been observed (Andersen et al., 2008). These include, for example, strong correlations between hippocampal volume and sexual abuse occurring during the ages of 3 years and 5 years, and between the ages of 11 years and 13 years; associations between corpus callosum area and sexual abuse occurring between the ages of 9 years and 10 years; and associations between frontal cortex area and sexual abuse occurring between the ages of 14 and 16 years (Andersen et al., 2008). Furthermore, in a longitudinal study in adults followed up from infancy, severity of CM, particularly abuse, experienced between the ages of 10 years and 11 years of age, was associated with larger right amygdala volume (Pechtel, Lyons-Ruth, Anderson, & Teicher, 2014). Right hippocampal volume, however, was positively associated with severity of exposure at both 7 years of age and 14 years of age (Pechtel et al., 2014).

In healthy children and adolescents, developmental changes in HPA activity occur, with the transition to adolescence or sexual maturation during adolescence being associated with significant increases in basal activity of the HPA axis (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Furthermore, age-related changes in glucocorticoid mRNA expression in cortical brain areas have been determined, with adolescence (i.e. relative to infants and the aged) being associated with increased glucocorticoid receptor mRNA levels in the prefrontal cortex (Perlman, Webster, Herman, Kleinman, & Weickert, 2007). These findings suggest increased sensitivity to glucocorticoids levels during adolescence, with potential subsequent effects on neuropsychological processing, neuroendocrine stress responsivity, and

vulnerability to psychopathology (Perlman et al., 2007). Postnatally, caregivers are thought to play a critical role in regulating the activity of the limbic-HPA system during infancy and early childhood (Gunnar & Donzella, 2002; Tarullo & Gunnar, 2006). For example, higher quality of maternal parental behaviour (i.e. maternal sensitivity and cooperation) has been shown to be associated with smaller increases in and better recovery in HPA axis activity in infants to mild everyday stressors, with less sensitive and more intrusive behaviours being associated with maintenance of higher cortisol levels for longer periods of time (Albers, Riksen-Walraven, Sweep, & Weerth, 2008). Furthermore, in adolescents for example, maternal behaviour, such as positive parenting, has been shown to be associated with structural development of the brain (Whittle, Yap, et al., 2009), reflected in attenuated volumetric growth in the amygdala, as well as enhanced cortical thinning in the orbitofrontal cortices over time (Whittle et al., 2014).

As indicated above, the brain undergoes critical changes during childhood and adolescence which are reflected in different patterns of maturation in a number of brain regions (e.g. cortical thickness increases with age in regions in the frontal cortex; higher order structures such as frontal lobe structures known to play a role in executive functioning, developing later) (Pechtel & Pizzagalli, 2011). It is well documented that early life adversity and stress have profound effects on vulnerable brain regions (e.g. HPA axis, prefrontal cortex, amygdala, and hippocampus) during childhood and adolescence (Pechtel & Pizzagalli, 2011; Teicher et al., 2003; Wilson, Hansen, & Li, 2011), and these effects are associated with deficits in neuropsychological functioning that may persist into adulthood (Hanson et al., 2013; Wilson et al., 2011).

2.4.6 Childhood maltreatment and neurocognition

It has been suggested that the HPA axis is the primary neurobiological mechanism that is affected in those with histories of early life stress or adversity (Gonzalez, 2013). HPA hyperactivation commonly affects particular brain regions, including the hippocampus, frontal cortex, and amygdala (Lupien et al., 2009). Impairments in these regions are frequently associated with deficits in neuropsychological functioning, including deficits in episodic and emotional memory (De Bellis, Woolley, & Hooper, 2013), executive functioning, attention, decision-making, and motor coordination (Pechtel & Pizzagalli, 2011).

There is evidence for the combined impact of clinical disorder (i.e. posttraumatic stress disorder) and CM history on a number of cognitive domains in children and adolescents, including visual episodic memory, executive functioning, and intelligence (Masson, East-Richard, & Cellard, 2015). Results from a recent systematic review indicated that a history of CM similarly impacts these aforementioned domains in children, adolescents and adults with CM histories, with deficits evident in verbal episodic memory, working memory, attention and executive function (Irigaray et al., 2013). That said, a few studies included in the aforementioned review found no significant differences in a number of domains between those with and without CM histories (Cicchetti, Rogosch, Howe, & Toth, 2010; De Bellis, Hooper, Woolley, & Shenk, 2010; Irigaray et al., 2013; Porter, Lawson, & Bigler, 2005). For example, Cicchetti and colleagues (2010) found no significant effect of CM on verbal learning and recall, and recognition memory, in children with and without CM histories. Similarly, De Bellis and colleagues (2010) reported no between-group differences in verbal memory, attention or IQ, in a large sample of children and adolescents with CM histories. Furthermore, controlling for both IQ and socio-economic status, Porter and colleagues (2005) found no significant differences in attention, concentration, learning and memory function, and academic performance, in sexually abused children and matched controls.

Despite a number of inconsistent findings, numerous independent studies have provided evidence for poorer neuropsychological functioning in youth exposed to CM. A history of CM in youth and adults has been found to impact a number of neuropsychological domains, including attention, language, verbal episodic memory, working memory, visuo-spatial skills, and executive functioning skills (De Bellis et al., 2013; Kavanaugh & Holler, 2014; Kirke-Smith, Henry, & Messer, 2014; Nadeau & Nolin, 2013; Nolin & Ethier, 2007; Spann et al., 2012). In addition, deficits in both intelligence and scholastic ability have been noted (De Bellis et al., 2013; Jones et al., 2004; Kavanaugh & Holler, 2014; Maguire et al., 2015; Mills et al., 2011; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Perez & Widom, 1994). Non-clinical adolescents with severe maltreatment histories demonstrate similar deficits, including poorer performance in learning and memory, executive function, processing speed, working memory, visuo-perceptual function and language (Vasilevski & Tucker, 2016).

Some studies have demonstrated closer associations between psychiatric disorder in traumatized individuals and neuropsychological deficits, than between trauma exposure and neuropsychological deficits (Saigh, Yasik, Oberfield, Halamandaris, & Bremner, 2006;

Schoeman, Carey, & Seedat, 2009). For example, in a sample of traumatized adolescents with and without PTSD, Schoeman and colleagues (2009) found that a diagnosis of PTSD, rather than trauma exposure alone, was associated with poorer performance in attention, nonverbal concept formation and visual memory. Similarly, in a sample of trauma-exposed older children and young adolescents, with and without PTSD, Saigh and colleagues (2006) noted that the presence of PTSD, and not trauma exposure alone, was associated with deficits in verbal IQ.

In addition to the aforementioned findings that have identified neuropsychological difficulties in those with maltreatment histories, some studies have demonstrated that maltreatment types, such as abuse and neglect, may have distinct cognitive impacts (DePrince, Weinzierl, & Combs, 2009). For example, in a community sample of children, DePrince and colleagues (2009) found that children exposed to familial trauma (i.e. physical and sexual maltreatment or witnessing domestic violence), relative to those exposed to non-familial trauma (i.e. natural disasters, motor vehicle accidents and/or community and peer violence) and non-trauma exposed children, demonstrated deficits in working memory, inhibition, processing speed and auditory attention. Furthermore, the cumulative effect of multiple forms of maltreatment on cognitive performance has been demonstrated, with, for example, abused, neglected children having significantly poorer executive function abilities than non-physically abused neglected children (Nolin & Ethier, 2007). The aforementioned studies provide support for the effect of familial trauma exposure on neuropsychological functioning, as well as the cumulative effect of multiple forms of maltreatment on neuropsychological performance (Nolin & Ethier, 2007).

2.4.7 Childhood maltreatment and emotion processing

Multiple brain structures which are known to be functionally interrelated are involved in mediating stress, anxiety, and fear-related behavior, and include the amygdala, hippocampus, orbitofrontal cortex, hypothalamus and the brain stem (Vermetten & Bremner, 2002). The frontal cortical areas modulate emotional responsiveness by inhibiting the functioning of the amygdala, with dysfunction in these regions likely underlying pathological emotional responses (Vermetten & Bremner, 2002). The amygdala is considered one of the central limbic structures associated with human response to affective stimuli, particularly fear-producing stimuli (Thomas, Drevets, Whalen, et al., 2001), and assigns affective significance to sensory events (Whittle, Yucel, & Allen, 2009). It has a wide-ranging pattern of reciprocal connections with cortical, limbic, monoaminergic and other brain regions associated with emotional,

autonomic, cognitive, and endocrine response to stress (Millan, 2003). Commonly, functional magnetic resonance imaging (fMRI) tasks depicting either facial expressions of emotion (i.e. fearful, neutral, happy, angry) or images depicting pleasant and unpleasant scenes or images, are used to assess emotion processing and to elicit activation in the amygdala and associated brain regions, in children, adolescents and adults (Britton, Taylor, Sudheimer, & Liberzon, 2006; Thomas, Drevets, Whalen, et al., 2001). Both explicit (i.e. emotion recognition or labelling of emotional stimuli) and implicit (i.e. passive viewing) emotion processing have been found to elicit activation in the amygdala, amongst other regions, however, results have been inconsistent (Habel et al., 2007). Some studies have reported more activation in the amygdala in response to explicitly processing emotional stimuli, relative to implicit processing (e.g. Fusar-Poli et al., 2009; Habel et al., 2007), while others have noted an increased probability of amygdala activation with implicit emotion processing (Costafreda, Brammer, David, & Fu, 2008). In healthy adolescents, amygdala activation is evident during the presentation of both happy and fearful faces (Van Den Bulk et al., 2013), as well as pleasant and unpleasant images (Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014), suggesting that the amygdala processes not only fear but general emotions as well (Hamann, Ely, Hoffman, & Kilts, 2002; Van Den Bulk et al., 2013; Yang et al., 2002). Similarly, in healthy adults, amygdala activation is associated with all emotional stimuli (i.e. both positive and negative) relative to neutral stimuli, however a greater probability of amygdala activation is associated with negative stimuli (e.g. fear and disgust) relative to positive stimuli (e.g. happiness) (Costafreda, Brammer, David, & Fu, 2008). Notably, in a clinical sample of adults (i.e. with depression and anxiety disorders) with CM histories, increased bilateral amygdala activity to emotional faces, in general, has also been observed (van Harmelen et al., 2013).

Developmental changes in emotion regulation have been demonstrated in healthy adolescents and young adults. Gee and colleagues (2013), using an emotional faces task, noted a valence shift in functional connectivity between the amygdala and medial prefrontal cortex, reflected in a positive coupling in early childhood and a more negative coupling with increased development, particularly during the transition to adolescence (Gee et al., 2013). Such valence shifts have important functional implications both for normal developmental changes as well as for differences in emotion regulation (Gee et al., 2013). Furthermore, in terms of amygdala-medial prefrontal cortex connectivity, amygdala development in early life is associated with more bottom-up signaling, and with more top-down signaling over time (Gee et al., 2013). Similarly, using images from the International Affective Picture System (IAPS, Lang, Bradley,

& Cuthbert, 1997) to assess emotion processing in a sample of healthy older children, adolescents and young adults, Vink and colleagues (2014) found that age was negatively associated with activation in the amygdala and hippocampus, and positively associated with activation in the ventrolateral pre-frontal cortex during emotion processing. These findings indicate that brain development from childhood to adulthood is associated with gradual increases in control of frontal regions over subcortical regions (Vink et al., 2014). Older adolescents may indeed demonstrate increased prefrontal cortex engagement during the processing of emotional stimuli, however, increased levels of sex hormones or gonadal hormones, such as testosterone, which increases dramatically from early to later adolescence, particularly in boys, may reduce prefrontal cortex-amygdala coupling, contributing to increased amygdala reactivity to threat (Spielberg et al., 2013). Such findings have also been noted in healthy women after a single dose of testosterone administration (van Wingen, Mattern, Verkes, Buitelaar, & Fernández, 2010). Early androgen excess in young adolescent boys is associated with a bias toward fearful faces (i.e. vs. happy faces), reflected in faster response times when rating threat, as well as significantly increased activations in the hippocampus in response to fearful vs. happy faces, compared with healthy controls (Mueller et al., 2009). Such findings suggest more difficulty in regulating negative emotion as puberty progresses (Spielberg et al., 2014). In addition, ovarian hormones (i.e. estradiol and progesterone), known to fluctuate during menstrual cycle phases, exert functional effects from early brain development and throughout both adolescence and adulthood. Ovarian hormone receptors are localized in brain regions commonly involved with the regulation of both cognition and emotion, and varying activation patterns across menstrual cycle phases have been noted during emotional processing in a number of brain regions, including the amygdala, medial prefrontal cortex, orbitofrontal cortex, dorsolateral prefrontal cortex, and inferior frontal gyrus (Toffoletto, Lanzenberger, Gingnell, Sundström-Promoa, & Comasco, 2014).

Maltreated children, such as those that have been neglected, demonstrate significantly lower levels of emotional understanding for negative emotions, and demonstrate significantly lower levels of adaptive emotion regulation skills, relative to non-maltreated children (Edwards, 2005; Kim & Cicchetti, 2010; Shipman, Edwards, Brown, Swisher, & Jennings, 2005). In addition, relative to non-maltreated children, neglected children report expecting significantly less maternal support and more maternal conflict to their emotional displays of negative emotions, and are also more inclined to attempt to suppress their expressions of negative emotion (Edwards, 2005; Shipman et al., 2005). Furthermore, maternal support has been found

to mediate the relationship between neglect and the child's emotional understanding (Edwards, 2005). Furthermore, it has been found that individual and multiple maltreatment types and earlier onset of maltreatment, are associated with emotion regulation difficulties and subsequent internalizing and externalizing behaviours and symptomatology in children (Kim & Cicchetti, 2010).

As indicated above, individuals with CM histories, relative to non-maltreated controls, demonstrate difficulties in emotion processing and regulation (Masten et al., 2008; Young & Widom, 2014). The amygdala is particularly vulnerable to early life stress and adversity given its high glucocorticoid receptor density (Peiffer, Barden, & Meaney, 1991). Caregivers, in particular, mothers, play an important role in regulating amygdala-prefrontal activity in children (Gee et al., 2014). A more optimal mother-child relationship is associated with a more developed pattern of amygdala-prefrontal connectivity, comparable with that of adolescents', as well as suppression of amygdala reactivity, underscoring the mother's role in modulating neurocircuitry during childhood (Gee et al., 2014). CM has been found to modify the regulatory ability of the brain's fear circuit, as demonstrated by Herringa and colleagues (2013), who determined that CM was associated with decreased hippocampus-subgenual cingulate resting-state functional connectivity in adolescents. In addition, the authors found lower amygdala-subgenual cingulate resting-state functional connectivity in females only, providing a possible explanation for female adolescents' vulnerability to the development of anxiety and depression (Herringa et al., 2013). Furthermore, the authors found that altered resting-state functional connectivity mediated the relationship between CM and anxiety and depression symptoms (Herringa et al., 2013).

In healthy adults, CM scores have been found to be positively and significantly associated with amygdala responsiveness to negative faces (i.e. those depicting fear and anger), and emotional abuse and neglect were found to be the strongest predictors of amygdala reactivity, followed by physical abuse and neglect, and sexual abuse (Dannlowski et al., 2012). A systematic review of facial emotion processing and recognition in maltreated children indicated that, in general, children with maltreatment histories were less accurate in facial tasks, demonstrated more reactivity, more response bias, and greater activation of particular brain regions, in response to facial tasks depicting negative emotions (da Silva Ferreira, Crippa, & de Lima Osorio, 2014). For example, it has been reported that children and adolescents with a history of caregiver deprivation and emotional neglect demonstrate significantly more amygdala and hippocampal

activation in response to processing fearful/angry faces, and are also faster in identifying threatening faces, relative to those without CM histories (Maheu et al., 2010). Similarly, previously institutionalized children, relative to controls, demonstrate significantly higher amygdala activation in response to fearful faces, relative to baseline (Tottenham et al., 2011), and children exposed to family violence demonstrate hyperactivation in the amygdala and insula, in response to angry faces, relative to neutral faces (McCrory et al., 2011). That said, in a sample of children, stressful life events (e.g. change in school, death of pet, birth of sibling) rather than traumatic life events (e.g. physical and sexual abuse, death of sibling, motor vehicle accident), were associated with increased amygdala activation to fearful, sad and happy faces, with traumatic life events being associated with enhanced activation in the amygdala to processing sad faces (Suzuki et al., 2014).

The majority of studies that have assessed emotion processing in youth with early life adversity have employed fMRI tasks depicting facial expressions of emotion, as reported above. Neuroimaging studies that have used fMRI tasks depicting positive and negative scenes or images from the IAPS (Lang et al., 1997) are few. Nonetheless, similar findings to the above have been reported. For example, employing pleasant and unpleasant images from the IAPS to assess emotion processing in adolescents, it was reported that CM was associated with increased activation in both amygdala and insula in response to negative, but not positive emotional stimuli (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). In addition, using images from the IAPS to assess emotion processing in adults with and without CM histories, it was found that a history of abuse or neglect was associated with significantly less accuracy in recognizing images, particularly positive and neutral images, but not negative images (Young & Widom, 2014).

It has been suggested that the insula cortex, which has dense bilateral connections with the amygdala, plays a role in emotional perception and the transmission of representations of affective sensory information to the amygdala (Whittle, Yucel, et al., 2009). Insula activation has been observed in healthy young adults in response to facial expressions of disgust (Phillips et al., 1997), disgust and happiness (Gorno-Tempini et al., 2001), and fear-inducing images (Schienle et al., 2002). Furthermore, insula activation has been found to be associated with recall-generated sadness and anticipatory anxiety (Reiman, 1997; Reiman et al., 1997). Children exposed to family violence, but with normative levels of anxiety and depression, demonstrate increased activation in the amygdala and the insula in response to angry faces, but

not sad faces (McCrory et al., 2011). Increased reactivity to salient stimuli in the amygdala and associated limbic regions is thought to represent an adaptive response to persistent environmental danger or threat, experienced in youth exposed to ongoing family violence or adversity (McCrory et al., 2011), yet, such heightened reactivity is likely not advantageous within safe environments, given the association between heightened reactivity in certain limbic regions (e.g. amygdala and insula) and risk for affective disorders (van Wingen, Geuze, Vermetten, & Fernández, 2011).

2.5 Dispositional traits: anxiety sensitivity and trait anxiety

2.5.1 Definition of anxiety sensitivity

It has been suggested that temperament or dispositional characteristics may be considered intermediate phenotypes for psychiatric disorders, reflecting sub-threshold clinical presentations (Altınbaş et al., 2015). Individuals with elevated levels of anxiety-related temperamental traits, such as those with high levels of AS or TA, may be termed ‘anxiety prone’, relative to those individuals with normative levels of anxiety (Simmons, Strigo, Matthews, Paulus, & Stein, 2006).

AS is defined as the individual’s fear of anxiety-related or arousal-related sensations and symptoms (Reiss & McNally, 1985), stemming from the individual’s belief that such sensations or symptoms may have negative or harmful physical, psychological/cognitive or social consequences, such as feelings of embarrassment, illness or added anxiety (Reiss, Peterson, Gursky, & McNally, 1986). McNally (2002) suggested that AS be considered the dread or fear of the sensations that commonly accompany fear, panic or anxiety (McNally, 2002), and thus, AS refers to the tendency of the individual to respond in a fearful manner to anxiety symptoms (McNally, 1989). Typical examples of such responses include believing that heart palpitations indicate an impending heart attack, or that a growling stomach or perspiring in public signals social evaluation and embarrassment for the individual (Olatunji & Wolitzky-Taylor, 2009; Reiss et al., 1986). In the presence of these experienced somatic symptoms, such as feeling dizzy, heart beating fast, feeling nauseas, the individual likely fears that these symptoms will have overwhelming consequences, such as going crazy or losing control (Reiss & McNally, 1985; Reiss, 1991). The expectation of such consequences results in elevated anxiety levels and the exacerbation of bodily symptoms, and leads to the vicious cycle that

culminates in a panic attack (Reiss & McNally, 1985; Reiss, 1991). Indeed, among a sample of college students, Hong (2010) found that heightened levels of AS cognitions, such as feeling scared or feeling fearful when certain anxious feelings and bodily sensations were experienced, were associated with elevated subsequent anxiety symptoms (Hong, 2010).

Reiss et al. (1986, page 2) suggested the following: “Anxiety sensitivity should increase alertness to stimuli signaling the possibility of becoming anxious, increase worry about the possibility of becoming anxious, and increase motivation to avoid anxiety-provoking stimuli” (Reiss et al., 1986). In response to feared adverse consequences, safety-seeking behaviours, which are primarily internal mental processes, such as escape and avoidance, are carried out (Clark, 1999). Anxiety is thus maintained as the individual is prevented from disconfirming his/her dysfunctional threatening beliefs (Clark, 1999; Heuer, Rinck, & Becker, 2007; Mowrer, 1960). Avoidant behaviour thus prevents improvement by eliminating the opportunity of exposure (Kiliç, Kiliç, & Yilmaz, 2008). Indeed, avoidance biases in clinically anxious children and adolescents have been found to be associated with youth anxiety severity, accounting for over 60% of the variance in clinician-rated anxiety (Kuckertz, Carmona, Chang, Piacentini, & Amir, 2015). In clinically anxious youths, self-rated fear has been found to be significantly associated with behavioural avoidance of aversive stimuli in youth with elevated levels of AS (Lebowitz, Shic, Campbell, Basile, & Silverman, 2015).

AS may be considered a dispositional characteristic or construct and an individual difference variable (McNally, 2002; Reiss et al., 1986). It has been suggested that the development and maintenance of AS is due to its relatively stable trait-like nature (Reiss & Haverkamp, 1996; Zavos, Gregory, & Eley, 2012), applicable also to the period of adolescence (Zavos, Rijdsdijk, & Eley, 2012). That said, AS has also been shown to develop as a function of social learning and learning experiences (Zavos, Gregory, et al., 2012), that, for example, bodily arousal may have potentially harmful effects (Olatunji & Wolitzky-Taylor, 2009; Stewart et al., 2001). In a sample of college students, Stewart and colleagues (2001) found that childhood learning experiences, which involved parental responses to both arousal-reactive symptoms (i.e. nausea, shortness of breath, racing heart, and dizziness) and arousal-non-reactive symptoms (i.e. encouraging colds, aches, pains, and rashes), had a direct influence on AS levels (Stewart et al., 2001). The authors therefore suggest that elevated AS may stem from the individual learning to catastrophize experienced bodily symptoms and conditions overall (Stewart et al., 2001). Additionally, exposure to negative parental behaviours, such as threatening, hostile and

rejecting behaviours, have been found to be associated with AS (Scher & Stein, 2003). Taken together, these findings highlight the role of both temperament and environment in AS.

2.5.2 Anxiety sensitivity and associated psychopathology

AS in youth and young adults is associated with a number of negative outcomes, including, impairment in daily life (Korte, Brown, & Schmidt, 2013), prolonged sleep onset latency (Weiner, Elkins, Pincus, & Comer, 2015), catastrophizing (Esteve & Camacho, 2008), fear of pain (Esteve & Camacho, 2008; Muris, Vlaeyen, & Meesters, 2001), eating disorder symptoms (Anestis, Holm-Denoma, Gordon, Schmidt, & Joiner, 2008), suicidal ideation (Capron, Allan, Ialongo, Leen-Feldner, & Schmidt, 2015), less engagement in vigorous-intensity exercise (Moshier et al., 2013), the later development of alcohol use disorder diagnoses (Schmidt, Buckner, & Keough, 2007), greater frequency of alcohol drinking for coping-related reasons (Novak, Burgess, Clark, Zvolensky, & Brown, 2003; Stewart & Zeitlin, 1995), and with various aspects associated with motives for alcohol and marijuana use and cigarette smoking (Comeau, Stewart, & Loba, 2001).

2.5.3 Anxiety sensitivity and anxiety symptoms and disorders

A meta-analytic review of 38 studies that evaluated AS in youth and adults with anxiety disorders, mood disorders and non-clinical controls, determined significantly higher levels of AS in those individuals diagnosed with an anxiety disorder, particularly panic disorder and posttraumatic stress disorder, relative to non-clinical controls (Olatunji & Wolitzky-Taylor, 2009). Furthermore, higher levels of AS overall were evident in those with anxiety disorders compared with those with mood disorders; age and biological sex played an important role in the relationship between AS and anxiety disorders; and different measures of AS seemed to moderate the effects of AS (Olatunji & Wolitzky-Taylor, 2009).

In terms of children and adolescents, a meta-analytic review of 15 studies of AS and child anxiety determined that AS in youth is a construct distinct from anxiety; that the relationship between AS and anxiety is stronger during adolescence than childhood; and that higher levels of AS are evident in youth diagnosed with an anxiety disorder relative to non-clinical youth (Noël & Francis, 2011). Furthermore, preliminary evidence was provided to suggest that youth

diagnosed with panic disorder, relative to other anxiety disorders, demonstrate higher levels of AS (Noël & Francis, 2011).

Longitudinal and cross-sectional studies have found that AS is associated with the development of DSM-IV anxiety disorder symptoms and subtypes (e.g. panic/agoraphobia symptoms) in non-clinical children and adolescents (McLaughlin et al., 2007; Schmidt et al., 2010), and is associated with spontaneous panic attacks and overall incidence of Axis I diagnoses, including anxiety, in non-clinical young adults (Schmidt, Zvolensky, & Maner, 2006). Furthermore, in non-clinical youth, the physical concerns subscale of the Childhood Anxiety Sensitivity Index (CASI, Silverman, Fleisig, Rabian, & Peterson, 1991) was found to be associated with all DSM-IV anxiety disorder subtypes; the social concerns subscale of the CASI was associated with generalized anxiety/overanxious disorder symptoms, social phobia symptoms and physical injury fears symptoms; and the psychological concerns subscale of the CASI was associated with obsessive-compulsive disorder symptoms, separation anxiety disorder symptoms, and panic/agoraphobia symptoms (McLaughlin et al., 2007). AS has also been found to be associated with symptoms of self-reported depression in healthy young adolescents and clinical samples of youth (Joiner et al., 2002; Muris et al., 2001), and has been shown to be associated with increased depressive symptoms over time in undergraduate students (Grant, Beck, & Davila, 2007). A reciprocal relationship over time between AS and depression has also been determined (Zavos, Rijsdijk, et al., 2012).

It has been suggested that either elevated AS precedes panic or that elevated AS may be due to the experiences that individuals have with panic attacks (Ginsburg, Lambert, & Drake, 2004). In a prospective study in a large sample of non-clinical young adults, it was found that experiences of panic, particularly spontaneous panic, and general stressors associated with anxiety symptoms, contributed to elevated AS (Schmidt, Lerew, & Joiner, 2000). Moreover, Zavos and colleagues (2012), in a longitudinal study in a sample of adolescent twin and sibling pairs, found that AS and anxiety demonstrated a reciprocal relationship during the adolescent period, with anxiety being a stronger correlate of AS than the opposite (Zavos, Rijsdijk, et al., 2012).

Previous research has reported that stressful life events during adolescence are associated with increases in AS over time. Zavos and colleagues (2012) reported that both independent (i.e. not due to the individual's behaviour) and dependent (i.e. due to the individual's behaviour)

stressful life events were associated with AS at final follow-up (i.e. time 3) in adolescent twin and sibling pairs (Zavos, Wong, et al., 2012). Furthermore, the cumulative effect of dependent, but not independent stressful life events, was associated with change in AS between time 2 and time 3 (Zavos, Wong, et al., 2012). Additionally, in a longitudinal study in a large community sample of adolescents, McLaughlin and colleagues (2009) reported that stressful life events, particularly those events associated with family discord (i.e. parental separation or divorce, family conflict) and physical health (i.e. serious illness or death), were associated with increases in AS over time (McLaughlin & Hatzenbuehler, 2009). AS in adolescents and young adults has been found to be positively and significantly associated with overall CM scores, particularly emotional and physical abuse scores (Martin, Viljoen, Kidd, & Seedat, 2014).

Given the above, AS in youth may be considered a cognitive risk factor for the development of anxiety symptoms, anxiety disorders, particularly panic symptomatology, panic disorder and agoraphobia (Ginsburg, Lambert, et al., 2004; Joiner et al., 2002; Kearney et al., 1997; Lau et al., 1996; McLaughlin et al., 2007; Muris et al., 2001), with adolescents demonstrating elevated levels of AS being particularly vulnerable to the development of anxiety symptoms and disorders (Noël & Francis, 2011). In a longitudinal study of young adolescents, Allan and colleagues (2014) determined three categories of adolescents, characterized by distinct anxiety symptom trajectories, namely, a small group characterized by high initial levels of anxiety that became elevated over time, and two larger groups characterized by moderate-declining and low-declining anxiety symptom trajectories, respectively (Allan et al., 2014). Notably, those adolescents with increased AS levels were more likely to be categorized in the smaller group exhibiting initially high anxiety symptoms that increased over time (Allan et al., 2014).

2.5.4 Definition of trait anxiety

Gregory and Eley (2007) provide clear definitions of both TA and state anxiety. TA refers to the relatively stable (i.e. over time and situation) individual differences in anxiety responsiveness, while state anxiety refers to temporary or transient anxiety symptoms that occur in response to events or situations that are perceived as threatening (Gregory & Eley, 2007). Spielberger and colleagues (1970) provide further clarification in their conceptualization of state and trait anxiety. “State anxiety (A-State) is conceptualized as a transitory emotional state or condition of the human organism that is characterized by subjective, consciously perceived feelings of tension and apprehension, and heightened

autonomic nervous system activity” (Spielberger, Gorsuch, & Lushene, 1970, p. 3). “Trait anxiety (A-Trait) refers to relatively stable individual differences in anxiety proneness, that is, to differences between people in the tendency to respond to situations perceived as threatening with elevations in A-State intensity” (Spielberger et al., 1970, p. 3).

Non-clinical adults with high levels of TA report significantly higher levels of somatic anxiety and demonstrate a more external locus of control than non-clinical adults with low levels of TA (Bennet & Stirling, 1998). In addition, high trait anxious adults report their mothers being significantly less caring and their parents being significantly more overprotective, than low trait anxious adults (Bennet & Stirling, 1998). TA in children is associated with child fearfulness, and both the mother’s level of fear and the mother’s fear expression, have been found to contribute to fearfulness in children (Muris et al., 1996). Furthermore, it has been demonstrated that TA in children is significantly and positively associated with TA levels of both the child’s parents (Muris et al., 1996). The development of TA in children is associated with parental child-rearing behaviour, for example, child TA has been found to be associated with parental inconsistency (Kohlmann, Schumacher, & Streit, 1988), and with perceived parental rearing styles characterized by rejection and overprotection, but not with emotional warmth (Markus, Lindhout, Boer, Hoogendijk, & Arrindell, 2003). In young college students, TA was significantly and positively associated with perceived parental psychological control, by both parents, and was negatively associated with subjective wellbeing (Seibel & Johnson, 2001). Furthermore, in a community sample of children and adolescents, TA was significantly and positively associated with somatic symptoms, such as headaches, low energy, sore muscles, and nausea (Garber, Walker, & Zeman, 1991).

As with AS, TA may be considered a dispositional construct or individual difference variable (McNally, 1989; Spielberger et al., 1970), and the development of TA is influenced by the individual’s environment (Kohlmann et al., 1988; Markus et al., 2003; Seibel & Johnson, 2001). Notably, despite TA and AS being closely associated (i.e. correlating significantly with one another) (Kiliç, Kiliç, & Yilmaz, 2008; Martin, Kidd, & Seedat, 2016; Muris, 2002), they are conceptually distinguishable from one another (McNally, 1989). Anxiety symptoms in high trait-anxious individuals should not induce fear, as is the case of AS, except if such symptoms are interpreted by the individual as being threatening (McNally, 1989). In addition, it has been determined that AS is predictive of variance in TA, and AS also predicts a significant amount of additional variance in fear, beyond that predicted by TA (Weems, Hammond-Laurence,

Silverman, & Ginsburg, 1998). That said, TA in adolescents and young adults has been found to predict AS (Martin et al., 2014). Moreover, both AS and TA predict unique proportions of variance in posttraumatic stress symptoms and anxiety disorder symptoms in children and adolescents, suggesting that AS and TA are distinct vulnerability factors, having independent predictive ability in anxiety disorder symptom development (Kiliç et al., 2008; Muris et al., 2001). Furthermore, whereas AS is more strongly associated with panic disorder symptoms and agoraphobia symptoms, TA is more strongly associated with separation anxiety disorder symptoms, social phobia symptoms, and depression symptoms in normal secondary school adolescents (Muris et al., 2001). Finally, the cognitive errors reflective of ‘incorrect’ or ‘negative thinking’ that are associated with AS, include, ‘catastrophizing’ and ‘personalizing’, whereas ‘overgeneralization’ is associated with TA, as found in a sample of children and adolescents with either anxiety or phobic disorders (Weems, Berman, Silverman, & Saavedra, 2001).

2.5.5 Trait anxiety and associated psychopathology

In non-clinical youth, TA is closely associated with both anxiety and depression symptomatology (Muris, 2002; Muris et al., 2001). For example, in healthy school-attending adolescents, Muris (2002) reported that TA correlated significantly with symptoms associated with DSM IV anxiety disorders, including panic disorder and agoraphobia; and with symptoms reflecting physiological manifestations of anxiety. Additionally, in healthy adolescents, TA correlated significantly (Muris et al., 2001) with self-reported depression. Furthermore, in healthy adolescents and young adults, heightened levels of TA have been shown to be uniquely and significantly associated with risk-avoidant decision-making (Maner et al., 2007) and risk avoidant orientation, as well as with negative risk appraisals, with, for example, trait anxious individuals perceiving negative outcomes as both serious and more probable (Maner & Schmidt, 2006).

In terms of trauma exposed youth, it has been reported that pre-trauma TA levels are associated with posttraumatic stress symptoms, generalized anxiety disorder symptoms, and post-trauma depressive symptoms (Weems, Pina, et al., 2007). TA has also been found to be associated with post-trauma somatic symptoms, including headaches, nausea/upset stomach, low energy, weakness and joint and limb pain, in trauma-exposed children, after controlling for child gender (Hensley & Varela, 2008).

TA levels in adults both with and without an anxiety disorder diagnosis are significantly and positively associated with childhood perceived stress, the presence of an adult anxiety disorder, (i.e. an panic disorder, specific phobia, and posttraumatic stress disorder), and with a greater probability of an anxiety disorder diagnosis in adulthood (Mundy et al., 2015). Furthermore, adults with panic disorder report poorer health-related quality of life, which is associated with TA, than do healthy controls (Kang et al., 2015).

Notably, as with AS, increases in TA are associated with stressful life events. For example, stressful events, such as those associated with romantic relationships, dissatisfaction with social activities, and worrying about the future, are significantly associated with increased TA in undergraduate students (Aktekin et al., 2001). Moreover, adversity experienced in childhood, such as childhood physical abuse, is associated with significantly higher levels of TA, as determined in outpatients with depressive and anxiety disorders, relative to non-abused outpatients (Handa, Nukina, Hosoi, & Kubo, 2008).

2.5.6 Anxiety proneness and neurocognition

There is strong evidence to indicate that young adults with anxiety disorders demonstrate poorer neuropsychological performance in a number of domains, including, attention, executive function, working memory and new learning, with cognitive dysfunction largely dependent on disorder subtype (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008). In comparison with the available literature reporting on neuropsychological performance in individuals with anxiety disorders, there have been relatively few studies that have examined important aspects of neuropsychological functioning, including memory, learning, executive functioning, intellectual functioning, and motor performance, in healthy adolescents with high levels of anxiety-related temperamental traits. Given the aforementioned, the impact of AP on neuropsychological performance in youth requires further exploration. Studies in adult samples indicate that certain anxiety-related temperamental traits, such as neuroticism and TA, are associated with poorer performance in working memory, verbal fluency, and IQ (Moutafi, Furnham, & Tsaousis, 2006; Sutin et al., 2011).

Attentional control theory proposes that automatic attention systems (i.e. those associated with limbic structures) in those with high levels of TA, exert a greater influence in directing attention than the more goal-directed, reflective attention systems (i.e. those associated with prefrontal

structures) (Eysenck, Derakshan, Santos, & Calvo, 2007; Ursache & Raver, 2014). High TA individuals demonstrate poorer recruitment of attentional control mechanisms and processes (Basten, Stelzel, & Fiebach, 2012; Bishop, 2009). Given that executive functioning is defined as a set of control processes that regulate an individual's thoughts and actions (Miyake & Friedman, 2012) to achieve a certain goal in a flexible way (Funahashi, 2001), it has been suggested that high TA is associated with poorer performance in executive functions associated with attention, inhibitory control, and shifting (Eysenck & Derakshan, 2011; Ursache & Raver, 2014). Indeed, elevated levels of TA have been found to be associated with poorer executive functioning in a sample of urban, low-income, predominantly African American children and pre-adolescents (Ursache & Raver, 2014). These findings are consistent with studies in high trait anxious adults that have reported deficits in executive function (e.g. such as poorer task shifting and inhibition), and demonstrate the association between high TA and deficits in the top-down control of attentional resources (Ansari, Derakshan, & Richards, 2008; Visu-Petra, Miclea, & Visu-Petra, 2012).

It has previously been demonstrated that tasks that assess executive function and memory abilities (e.g. working memory, verbal and visual memory, and immediate and delayed memory) are highly correlated and share a common underlying executive attention element (Duff, Schoenberg, Scott, & Adams, 2005; McCabe, Roediger III, McDaniel, Balota, & Hambrick, 2010). Furthermore, IQ is strongly associated with both executive function and memory abilities (Duff et al., 2005). High levels of AS are associated with deficits in working memory. For example, undergraduate students with elevated levels of AS demonstrate significantly poorer performance on a verbal working memory task, relative to students with low levels of AS, however, neither performance on a math fluency task nor performance on a psychomotor task appear to be affected by AS levels (Barnard, Broman-Fulks, Michael, Webb, & Zawilinski, 2011). Elevated TA is associated with poorer working memory performance, and poorer academic performance (e.g. spelling and mathematics abilities, English, verbal- and non-verbal reasoning) in school attending children (Owens, Stevenson, Hadwin, & Norgate, 2012; Owens, Stevenson, Norgate, & Hadwin, 2008). Furthermore, TA in healthy young adults is associated with restricted working memory capacity (MacLeod & Donnellan, 1993; Qi et al., 2014).

Visual working memory deficits have been found to be associated with symptoms of anxiety and depression in normal school children (Aronen, Vuontela, Steenari, Salmi, & Carlson,

2005). In a large sample of children, Lundy and colleagues (2010) found that increased anxious/depressed symptomatology was significantly associated with a range of neuropsychological measures. Those children with elevated anxious/depressed symptomatology demonstrated deficits in the domains of both verbal and non-verbal intellectual functioning, attention, executive functioning, language, processing speed, psychomotor speed, visual construction skills, and aspects of verbal learning and memory (Lundy, Silva, Kaemingk, Goodwin, & Quan, 2010). Additionally, anxious/depressed symptoms were associated with poorer abilities or skills in mathematics, spelling and reading (Lundy et al., 2010).

2.5.7 Anxiety proneness and emotion processing

Youth with anxiety disorders commonly demonstrate an attentional bias towards threatening stimuli or information, however, some studies have reported a bias away from threat, and some have reported no significant threat bias at all (Bar-Haim et al., 2007; Roy, Dennis, & Warner, 2015). Nevertheless, biases commonly associated with clinically anxious youth can broadly be categorized into three types of biases. These include, an attentional bias to threat (i.e. the tendency to allocate attention to threat-related stimuli or to have delayed disengagement from threat-related stimuli), interpretation bias (i.e. the tendency to interpret ambiguous situations as more threatening), and memory bias (i.e. the tendency to demonstrate greater memory for information about danger and threat) (Bögels & Zigterman, 2000; Eysenck, Derakshan, Santos, & Calvo, 2007; Muris & Field, 2008; Watts & Weems, 2006). It is thought that such biases play a key role in both the aetiology and maintenance of anxiety disorders and anxious states (Bar-Haim et al., 2007; Hofmann, Ellard, & Siegle, 2012; Roy et al., 2015), as threat biases aid in the reinforcement and maintenance of avoidance of the feared stimulus, which in turn prevents the extinction of the feared stimulus (Mowrer, 1960). Increased reactivity to either stress-related or threat-related stimuli, particularly evident in clinical and AP individuals, is manifested neurally, with increased activation commonly evident in brain regions associated with emotion processing (e.g. the amygdala), and decreased activation evident in regulatory circuits (e.g. the prefrontal cortex) that play critical roles in attenuation of bottom-up emotional processes (Hofmann et al., 2012; Ochsner et al., 2009; Paulus, 2011).

Threat biases are frequently evident in AP youth (Bar-Haim et al., 2007; Puliafico & Kendall, 2006). AS levels in non-clinical youth have been found to be positively and significantly

associated with attentional bias for both general threat images, as well as pain-related images (Schoth, Golding, Johnson, & Liossi, 2015). Furthermore, AS has been found to be associated with pain-related images, but not general threat images, suggesting that AS in youth is closely associated with an attentional bias for personally relevant negative stimuli (Schoth et al., 2015). High trait anxious children also demonstrate greater threat-related interference on anxiety-related words (i.e. in an emotional Stroop task), and have more difficulty discriminating happy from angry facial expressions when the happy facial expressions reflect low levels of emotion (Richards, French, Nash, Hadwin, & Donnelly, 2007). High trait anxious youth also demonstrate an attentional bias toward angry faces, relative to neutral faces (Telzer et al., 2008).

fMRI studies in individuals with anxiety disorders (i.e. posttraumatic stress disorder, social anxiety disorder and specific phobia) have reported altered amygdala and insula functioning in response to processing negative emotional stimuli (Etkin & Wager, 2007). Similarly, relative to healthy controls, adults with a diagnosis of generalized anxiety disorder, panic disorder, or social anxiety disorder, demonstrate enhanced amygdala activation in response to matching fearful vs. happy facial expressions, and fearful faces vs. baseline condition, with greater activation in the amygdala being associated with higher levels of TA (Fonzo et al., 2015). Notably, enhanced insula activity to all emotional faces (i.e. angry, fearful, and happy), as well as to processing angry vs. happy faces, was found to be unique to the panic disorder group in the aforementioned study (Fonzo et al., 2015).

Enhanced amygdala activation in response to masked and non-masked negative emotional stimuli (i.e. non-masked angry and fearful faces, and masked angry faces) has been reported in youth with anxiety disorders, such as generalized anxiety disorder and panic disorder (McClure et al., 2007; Monk et al., 2008; Thomas, Drevets, Dahl, et al., 2001). Furthermore, youth with anxiety disorders, such as generalized anxiety disorder, relative to controls, demonstrate reduced negative coupling between the amygdala and ventrolateral prefrontal cortex (Monk et al., 2008). In youth, the degree of activation in the amygdala in response to negative stimuli (i.e. masked angry faces, and non-masked fearful faces relative to neutral faces) has been found to correlate with anxiety symptom severity (Monk et al., 2008; Thomas, Drevets, Dahl, et al., 2001).

fMRI studies have reported that high anxious individuals commonly demonstrate deficits associated with the activation of the amygdala, as well as deficits associated with amygdala coupling with various brain regions in response to processing emotional material (Sandi & Richter-Levin, 2009). For example, healthy trait anxious adults demonstrate reduced coupling of limbic responses to passively viewing fearful, happy and neutral faces (Mujica-Parodi et al., 2009). AP young adult students, relative to anxiety normative students, demonstrate increased amygdala and insula reactivity in response to viewing emotional faces, such as angry, fearful, and happy faces, with increased amygdala (i.e. predominantly left amygdala) and bilateral insula activation being associated with elevated levels of AS, TA, and neuroticism (Stein, Simmons, Feinstein, & Paulus, 2007). Findings of increased amygdala and insula activation in response to negative stimuli in AP individuals, as reported by Stein and colleagues (2007), are in line with Dilger et al. (2003) that reported increased amygdala and insula activation in response to phobia-relevant visual stimuli, in young adult spider phobics, relative to controls (Dilger et al., 2003). As suggested by Stein et al. (2007), increased amygdala and insula activation to emotional stimuli in AP individuals, may represent a functional endophenotype for vulnerability to the development of anxiety disorders.

Some inconsistent findings to those determined by Stein et al. (2007) have been reported. For example, in an fMRI study in which insula responses to fear-related stimuli were assessed in healthy adults and adults with specific animal phobia, controlling for both trait and state anxiety, significant positive correlations between AS scores in the total sample and activation of the right insula were reported, however, no significant correlation was determined between AS scores and left insula or either amygdala (Killgore et al., 2011). Furthermore, higher levels of TA in healthy young adults were found to correlate with increased amygdala activation in response to both unattended and masked negative stimuli (i.e. unattended fearful faces and masked fear) (Dickie & Armony, 2008; Etkin et al., 2004), however, no association was determined between TA levels and activation in either the amygdala or hippocampus in response to non-masked fear (Etkin et al., 2004). Nevertheless, in non-clinical students, increased activation in the amygdala and insula in response to both anticipating and viewing aversive images, has been reported (Nitschke, Sarinopoulos, MacKiewicz, Schaefer, & Davidson, 2006), and increased activation in the insula in response to anticipating aversive stimuli has been found in AP students (Simmons et al., 2006).

2.6 Genetics: childhood maltreatment and anxiety proneness

2.6.1 Heritability of anxiety sensitivity

Heritability is defined as the proportion of phenotypic variance due to genetic factors (Smoller & Tsuang, 1998). Previous studies in children, adolescents and adults report that AS is moderately heritable (Eley et al., 2007; Jang, Stein, Taylor, & Livesley, 1999; Stein et al., 1999; Taylor, Jang, Stewart, & Stein, 2008; Zavos et al., 2010). Eley and colleagues (2007) estimated heritability at 37% in their sample of 576 (i.e. 96 monozygotic and 192 dizygotic pairs) 8 year old children. Zavos and colleagues (2010) estimated heritability at 43% and 34% at two time points in a large sample of adolescents (i.e. monozygotic and dizygotic twin and sibling pairs) with a mean age of 15 years and 17 years at each time point, respectively. Furthermore, Stein and colleagues (1999) estimated heritability at 45% in a sample of 674 (i.e. 179 monozygotic and 158 dizygotic twin pairs) adults. The authors found that additive genetic effects (i.e. accounting for 45% of the total variance in AS) as well as unique environmental effects (i.e. accounting for 55% to 89% of AS total and subscale scores) primarily influenced AS. In a community sample of 337 twin pairs (i.e. 179 monozygotic and 158 dizygotic), Jang and colleagues (1999) determined that the heritability of AS factors (i.e. physical, control and social concerns) was stronger in women, with AS factors being heritable only in women and accounting for between 37% and 48% of the total variance. In men, environmental factors accounted for all the variability (Jang et al., 1999). More recently, in a larger adult sample of 438 twin pairs, Taylor and colleagues (2008) determined that for women, each dimension of AS (i.e. physical, cognitive, and social concerns) was influenced by a combination of both genetic and environmental factors, with heritability in women significantly increasing with AS scores. In terms of men, AS dimensions were found to be influenced only by environmental factors (Taylor et al., 2008).

2.6.2 Heritability of trait anxiety

Legrand and colleagues (1999) assessed the heritability of TA in a large sample of 574 child and adolescent twin pairs and determined that TA is moderately heritable, estimated at 45%, with the remaining variance attributable to non-shared environmental influences and measurement error. Similarly, in a sample of 1058 child and adolescent twins, Lau and colleagues (2006) found moderate genetic effects on TA (31%), substantial non-shared

environmental effects (54%), and minimal shared environmental effects (15%). More recently, Garcia and colleagues (2013) assessed changes in both genetic and environmental influences on TA during middle adolescence and early adulthood (i.e. at ages 14 years, 18 years, and 21 years) in a large sample of same-sex twin pairs, and reported increased heritability of TA with age during middle to late adolescence, with genetic influences being strongly correlated across the aforementioned ages, providing evidence for stable genetic influences on TA during adolescence. Furthermore, decreased shared environmental effects across adolescence were noted, while non-shared environmental effects were moderately stable over time and were found to be age-specific (Garcia et al., 2013). TA has also been found to be relatively stable across early and later adulthood (Usala & Hertzog, 1991; Watson & Walker, 1996).

2.6.3 The serotonin transporter gene

Much of the genetic research associated with childhood anxiety has focused on a functional polymorphism in the promoter region of the serotonin [5-hydroxytryptamine (5-HT)] transporter (5-HTT) gene (gene, *SLC6A4*; variant, 5-HTTLPR) (Murray et al., 2009; Stein, Campbell-Sills, & Gelernter, 2009). The long (L) and short (S) variant of the 5-HTTLPR genotype have been found to have different effects on the expression and function of 5-HTT (Greenberg et al., 1999), with the *S*-allele being associated with lower transcriptional efficiency, and subsequent reduced expression of 5-HTT, relative to the *L*-allele (Lesch et al., 1996; Smoller, 2008). Both animal and human studies have reported that the experience of early adversity, such as CM or early life stress, is associated with reduced 5-HT function, suggestive of a dysregulated serotonergic system (Kaufman et al., 1998; Maestripieri et al., 2006; Miller et al., 2009). In the adult human brain, serotonergic raphe neurons project to a number of brain regions, (e.g. the cortex, hippocampus, and amygdala), with neurotransmission mediated by 5-HT, which acts as a modulator of emotional and physiological functioning in the central nervous system, and also plays a key role in motor function, pain, circadian and neuroendocrine functions, and the integration of emotion and cognition (Lesch et al., 1996; Lesch & Mössner, 1998; Watts-English, Fortson, Gibler, Hooper, & De Bellis, 2006).

It has been suggested that stable traits, such as AS and TA, are more closely associated with risk genes than overt symptoms or behaviours (Garcia et al., 2013; Iacona, Malone, & McGue, 2008). An earlier study reported that individuals with one or two copies of the *S*-allele of the 5-HTTLPR polymorphism, relative to those homozygous for the *L* variant, demonstrated

higher neuroticism scores, known to be associated with both anxiety and depression (Lesch et al., 1996). Support for this finding was provided in a meta-analysis in which the *S*-allele was found to be significantly associated with a measure of neuroticism (Schinka, Busch, & Robichaux-Keene, 2004).

A meta-analysis of 22 studies revealed that the *S*-allele was associated with a predisposition to anxiety, with significant associations evident between the 5-HTTLPR polymorphism and avoidance traits (Munafo et al., 2003), such as harm avoidance (Katsuragi et al., 1999). Furthermore, the *S*-allele has been found to be associated with lower levels of resilience in undergraduate students (Stein, Campbell-Sills, & Gelernter, 2009), and with increased state and TA, general anxiety, depression, obsessive-compulsive disorder symptoms, a likelihood of manifesting neurotic symptoms, guilt, hostility and aggression, and decreased self-directedness, in healthy non-clinical female adults (Gonda et al., 2009). In healthy male undergraduates, the *SS* genotype was associated with significantly higher levels of TA than the *L*-allele (Zhang, Liu, Li, Song, & Liu, 2015). Moreover, the *S*-allele is associated with anxiety disorders, such as obsessive-compulsive disorder (Lin, 2007), posttraumatic stress disorder (Koenen et al., 2009; Lee et al., 2005; Xie et al., 2009), sub-threshold anxiety (Gonda, Rihmer, Juhasz, Zsombok, & Bagdy, 2007), yet, findings in panic disorder have been more inconsistent (Blaya, Salum, Lima, Leistner-Segal, & Manfro, 2007). Furthermore, there is evidence for an association between the *L*-allele and increased anxiety in adolescents (Jorm et al., 2000) and shyness in children (Arbelle et al., 2003); and in adults, the *L*-allele has been found to be associated with neuroticism, harm avoidance, anxiety and depression (Brummett et al., 2003; Katsuragi et al., 1999; Long et al., 2013).

The *S*-allele or *SS* genotype is reportedly differentially associated with risk for psychopathology in males and females. Findings from a recent systematic review determined that the *S*-allele or *SS* genotype was associated with an increased risk of depression, depression symptoms, anxiety traits, anxiety symptoms, as well as symptoms of internalizing behaviours, in females (Gressier, Calati, & Serretti, 2016). In contrast, the *S*-allele or *SS* genotype was associated with an increased risk of aggressiveness, conduct disorder and increased externalizing behaviours, in males (Gressier et al., 2016). Notably, the authors suggested that stressful life events appeared to strengthen the aforementioned associations (Gressier et al., 2016). Indeed, the 5-HTTLPR polymorphism has been found to interact with stressful life events to increase susceptibility to depressive symptoms, onset of depression, clinical

depression, depression severity, and suicidality (Caspi et al., 2003; Wilhelm et al., 2006; Zalsman et al., 2006). A few studies, however, have not supported this finding (Gillespie, Whitfield, Williams, Heath, & Martin, 2005; Surtees et al., 2006). Nonetheless, in studies where significant associations have been determined, it was found, for example, that female adolescent *SS* genotype carriers were at increased risk for depression if they had experienced more adverse life events (e.g. illness, failed relationships, death/loss, unemployment) and family social adversity (e.g. financial, work, and social difficulties) (Eley et al., 2004). Moreover, children with the *S*-allele were found to be more vulnerable to depression if they had experienced significant stress, such as maltreatment (Kaufman et al., 2004). In a sample of adolescents with early life institutional deprivation, *S*-allele carriers had a higher level of emotional problems, relative to *L* homozygotes (Kumsta et al., 2010). In addition, adolescents who were both *SS* genotype carriers and reported more stressful life events (e.g. being mugged, assaulted, beaten up, rejected and bullied by peers, death of parent) between the ages of 11 and 15 years, demonstrated the largest increases in emotional problems (Kumsta et al., 2010). In a sample of panic disorder patients and healthy controls, *SS* homozygotes who reported more separation life events (e.g. death of child, spouse or family member, divorce, and separation from a significant person) demonstrated a higher prevalence of panic disorder, as well as harm avoidance (Choe et al., 2013). In contrast to the above, an interaction effect of the *LL* genotype and greater levels of family adversity (e.g. overcrowding, parental delinquency, marital discord, unwanted pregnancy) on anxiety and depressive disorders in young adults, was determined (Laucht et al., 2009). Nonetheless, the findings above suggest that the 5-HTTLPR polymorphism interacts with stressful life events to increase susceptibility to psychopathology.

With particular relevance to the current study, Stein and colleagues (2008) investigated whether the 5-HTTLPR genotype and CM scores would interact to increase susceptibility to AS in undergraduate students. They reported a significant interaction between 5-HTTLPR genotype and CM (i.e. specifically child abuse), with *SS* genotype carriers who reported higher levels of CM, having significantly higher levels of AS, relative to *L*-allele carriers (Stein, Schork, & Gelernter, 2008). In contrast, Klauke and colleagues (2011) reported a significant interaction between 5-HTTLPR genotype and CM on AS, with healthy young adult *LL* genotype carriers who reported high levels of CM, demonstrating elevated levels of AS (Klauke et al., 2011).

Please see Appendix A1: Hemmings, S.M.J, Martin, L.I., van der Merwe, L., Benecke, R., Domschke, K., & Seedat, S. (2016). Serotonin transporter variants play a role in anxiety

sensitivity in South African adolescents. Published in *The World Journal of Biological Psychiatry*, 17(1), 66-75.

2.6.4 Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF) is a secretory protein in the neurotrophin family that influences the proliferation, survival, differentiation and repair of neuronal cells in the peripheral and central nervous system (Bath & Lee, 2006). Furthermore, it has been suggested that BDNF protects against stress-induced neuronal damage (Bergström, Jayatissa, Mørk, & Wiborg, 2008). BDNF is widely expressed in the mammalian brain, at highest levels in the hippocampus and cerebral cortex (Huang & Reichardt, 2001; Schmidt-Kastner, Wetmore, & Olson, 1996) and is known to enhance hippocampal long-term potentiation, a form of synaptic plasticity, which is associated with both memory and learning efficiency (Yamada, Mizuno, & Nabeshima, 2002). The gene encoding BDNF contains a functional single nucleotide polymorphism (SNP) resulting in a valine-to-methionine substitution at amino acid 66 (*Val66Met*, rs6265) in the 5' pro-BDNF domain (Egan et al., 2003; Hemmings et al., 2013). Relative to the *Val66* allele, the *Met66* allele is associated with a decrease in activity-dependent secretion of BDNF (Egan et al., 2003).

There is evidence to suggest that mood and anxiety disorders are associated with lower serum BDNF levels. For example, relative to controls, significantly lower BDNF levels have been observed in depressed individuals (Molendijk et al., 2014), as well as those meeting criteria for posttraumatic stress disorder (Angelucci et al., 2014). In addition, the BDNF *Val66Met* polymorphism has been found to be associated with generalized anxiety disorder (Moreira et al., 2015), obsessive-compulsive disorder, (Hemmings et al., 2008), posttraumatic stress disorder (Bruenig et al., 2016), and with bipolar disorder and schizophrenia, in particular (Gatt, Burton, Williams, & Schofield, 2015), however, inconsistent findings have been reported (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia, 2008; Notaras, Hill, & van den Buuse, 2015; Verhagen et al., 2010; Wang et al., 2015).

Animal and human studies have reported that both acute and chronic stress are associated with decreased levels of BDNF, potentially resulting in the enhancement of anxiety-related behaviours (Chen et al., 2006; Mitoma et al., 2008; Murakami, Imbe, Morikawa, Kubo, & Senba, 2005; Suzuki et al., 2014). Stressful life events, such as CM, have been found to be

associated with reduced serum BDNF levels in adults (Elzinga et al., 2011). For example, Elzinga and colleagues (2011) found that exposure to CM was associated with decreased BDNF serum levels in *Met66* allele carriers, in a sample of adults with lifetime major depressive disorder (Elzinga et al., 2011). In line with these findings, children and adolescents with CM histories, such as those that have experienced sexual abuse, demonstrate significantly lower serum BDNF levels than non-trauma exposed youth, with multiple sexual abuse experiences being associated with the lowest serum BDNF levels (Şimşek, Yüksel, Kaplan, Uysal, & Alaca, 2015).

There is some evidence to suggest that the BDNF *Val66Met* polymorphism is associated with certain personality traits, including TA, neuroticism, harm avoidance, and introversion (Lang et al., 2005; Montag, Basten, Stelzel, Fiebach, & Reuter, 2010; Sen et al., 2003; Terracciano et al., 2010), although not all studies have reported such associations (Terracciano et al., 2010; Willis-Owen et al., 2005). Furthermore, the *Met66* allele has previously been found to be associated with increased anxiety-related behaviours (Chen et al., 2006), and greater likelihood of an anxiety disorder in youth (Tocchetto et al., 2011), however, the *Val66* allele has also been found to be associated with greater neuroticism scores, and greater levels of anxiety in youth in the presence of high levels of stress (Chen, Yu, Liu, Zhang, & Zhang, 2015; Frustaci et al., 2008).

A number of previous studies have found significant gene-environment (e.g. BDNF x stressful life events) interaction effects on vulnerability to psychopathology in youth. For example, in a sample of non-clinical adolescents, a significant BDNF x early childhood trauma intensity (i.e. physical and sexual abuse, significant parental conflicts, death, severe illness) interaction effect on guilt proneness was determined, with trauma intensity being positively associated with guilt proneness in *Met66* allele carriers (Szentágotai-Tótar et al., 2015). Furthermore, in young adults with and without a diagnosis of lifetime major depression, a significant BDNF x early life adversity (e.g. physical and verbal abuse, parental conflict, observed violence in the home) interaction effect on lifetime major depressive disorder was found, with *Met66* allele carriers with more early life adversity, demonstrating a greater likelihood of major depressive disorder (Carver, Johnson, Joormann, Lemoult, & Cuccaro, 2011). In line with these findings, a significant BDNF x CM interaction effect on depression symptoms was determined in a sample of healthy young adults, with *Met66* allele carriers who had experienced more

childhood sexual abuse, having a greater amount of depressive symptoms (Aguilera et al., 2009).

In adult samples, similar significant BDNF x stress (i.e. early life stress and negative life stressors) on harm avoidance, as well as amygdala and hippocampal volumes, have been determined, with *Met66* allele carriers being most affected (Gatt et al., 2009; Kim et al., 2009). That said, contrasting results have also been reported, with, for example, some gene-environment studies finding significant interaction effect of the higher functioning *Val66* allele and environmental exposure on psychopathology in youth and young adults, such as increased neuroticism and depressive symptoms (Chen, Li, & McGue, 2013; Lehto, Maestu, Kiive, Veidebaum, & Harro, 2016). Notably, Lehto and colleagues (2016) found a significant BDNF x recent stressful life events on neuroticism in young adults, but no BDNF x childhood adversity on neuroticism was determined.

Given that no published studies to date have explored the interactive effect of the BDNF *Val66Met* and CM on AP (i.e. combined AS and TA scores), further research is warranted so as to provide a clearer understanding of the possible genetic and environmental mechanisms underlying the development of AP.

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CHAPTER 3

METHODS

This study was a two-tier study in a non-clinical sample of secondary school students.

3.1 Tier 1

3.1.1 Rationale for Tier 1

The first tier of the research was conducted so as to screen a large number of secondary school students, representative of those attending secondary schools in Cape Town, in order to determine, in particular, levels of both self-reported childhood maltreatment (CM) [as measured with the Childhood Trauma Questionnaire (CTQ-SF, Bernstein et al., 2003)] and anxiety proneness (AP) [determined by levels of both anxiety sensitivity, as measured with the Childhood Anxiety Sensitivity Index (CASI, Silverman, Fleisig, Rabian, & Peterson, 1991) and trait anxiety, as measured with the trait version of the State-Trait Anxiety Inventory (STAI, Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983)] in the sample. In addition, salivary DNA was provided by participants for genetic analysis. With the aim of including approximately 100 participants in tier 2, with high and low levels of CM and AP respectively, the participants included in the first tier (i.e. approximately 1000 participants), based on their self-reported levels of CM and AP, provided a large sample from which the tier 2 participants were selected.

3.1.2 Research design

The tier 1 part of the study constituted a cross-sectional survey and utilized a stratified, two-stage cluster sampling design to obtain a cross-sectional sample of secondary school students through public secondary schools.

3.1.3 Sampling methodology

With the goal of sampling approximately 1000 secondary school students that were both ethnically and socio-demographically representative of the public secondary school population in Cape Town, the study employed a stratified two-stage cluster sampling design. The four

educational districts in Cape Town (i.e. Metro North, Metro South, Metro East and Metro Central), as indicated by the Western Cape Education Department, were regarded as strata, and the associated schools, as clusters within each strata, from which students were sampled (Carlin & Hocking, 1999; Waters, Salmon, Wake, Wright, & Hesketh, 2001). Prior to randomly selecting secondary schools and students from these schools, the total population of public secondary schools and the total population of students from these secondary schools, from the four educational districts, was determined. At stage 1, 16 secondary schools within the educational districts were selected at random with probabilities proportional to school size, so as to include approximately 1000 students in the study. Subsequently, at the second sampling stage, 60 students (i.e. 12 students from each of the five grades, namely, grades 8, 9, 10, 11, and 12) were selected at random from class lists provided by participating schools to participate in the study. However, due to an initial low response rate, additional schools and students were subsequently selected, using above procedures, for inclusion in the study. A total of 1149 participants from 29 secondary schools participated in the first tier of the study. See Table 1.

Table 1

Tier 1 sampling methodology.

Educational district	Population of schools (2010)	Population of students (2010)	Proportional allocation	No. of schools with 60 students per school	No. of schools sampled overall	No. of students sampled overall
Central	42	30579	265	4	7	240
East	29	34437	298	5	9	334
North	30	29013	251	4	8	382
South	23	21372	185	3	5	193
Total	124	115401	999	16	29	1149

For a description of the sample, procedure, instruments and tier one outcomes, please see Appendix A2: Martin, L., Viljoen, M., Kidd, M., & Seedat, S. (2014). Are childhood trauma

exposures predictive of anxiety sensitivity in school attending youth? Published in Journal of Affective Disorders, 168, 5-12.

3.2 Tier 2

3.2.1 Research design

The second tier comprised a cross-sectional study, utilizing quantitative methods.

3.2.2 Participant selection and categorization

Participants were included in the second tier of the study based on self-reported levels of both CM and AP, established from data collected in the 1st tier. Subsequently, four groups of adolescents were randomly selected for participation in the 2nd tier, based on the aforementioned levels, and were matched as closely as possible on tier 1 age, ethnicity, gender, and tier 1 educational status (i.e. current grade at school).

Group status was initially determined by selecting participants who fell within the upper 66th and lower 33rd percentile (i.e. high and low) for both CM and AP, respectively. Once all second tier data had been collected, tier 2 group status was re-calculated by grouping participants on their tier 1 CM status (i.e. either high or low) and using the 50th percentile of their tier 2 AP score to determine high and low AP status. See Table 2 for group categorization, number of participants included per group, and self-reported ethnicity.

Table 2

Tier 2 group categorization and self-reported ethnicity (N=111).

	Group			
	low CM - low AP (n=34, 30.6%)	low CM - high AP (n=27, 24.3%)	high CM - low AP (n=22, 19.8%)	high CM - high AP (n=28, 25.2%)
Ethnicity (count, % of group)				
African	22 (64.7)	24 (88.9)	15 (68.2)	25 (89.3)
Mixed race	12 (35.3)	3 (11.1)	6 (27.3)	3 (10.7)
Other	0	0	1 (4.5)	0

The tier 2 sample consisted of 111 healthy adolescents. All participants were right-handed. Of the 111 participants included in the study, 104 underwent neuropsychological testing and 98 functional neuroimaging.

Eligible adolescents were (1) between 13 and 18 years of age, (2) able to read, write, and understand either English or Afrikaans at 5th grade level, (3) not currently taking any psychopharmacological medications, (4) willing and able to provide written informed assent, (5) medically well enough to undergo both neuropsychological testing and functional MRI scanning, and (6) willingness for female adolescents to undergo a pregnancy test.

Exclusion criteria included: (1) receiving treatment for an anxiety disorder, (2) a current mood or anxiety disorder diagnosis, (3) a current or past history of bipolar disorder, schizophrenia or other psychotic disorders, or childhood disorders (i.e. attention deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder), (4) a current history of alcohol or substance abuse or dependence, (5) previous head trauma, (6) current psychotropic medication use, (7) and pregnancy.

In terms of the MRI scanning, participants were excluded if they had a cardiac pacemaker, any metal prosthesis or pin(s), clips on blood vessels, inner ear prosthesis, or if they were currently pregnant. Furthermore, prior to the MRI scanning, participants removed all metal objects, including jewellery and hair pins.

3.2.3 Procedures

The study was approved by the Health Research Ethics Committee of Stellenbosch University (ethics reference number: N10/11/370), Cape Town, South Africa. All adolescents who participated in the second tier of the study were assessed at the Department of Psychiatry, Stellenbosch University, and were invited to attend up to three study visits.

Participants took part in (1) a neuropsychiatric assessment, (2) a brief medical examination, (3) a genetics blood draw, (4) a neuropsychological assessment, and (5) structural (and functional neuroimaging (fMRI)). For the purposes of the study's aims, the structural MRI data is not included within this dissertation. The above-named assessments aimed to explore the relationships and interactions between childhood trauma, neuropsychological deficits, neural circuitry, and anxiety proneness in both high- and low-anxiety prone adolescents. Assessments were conducted by a research psychologist trained in all measures (L. Martin), overseen by a clinical psychologist based at the Department of Psychiatry, Stellenbosch University.

Visit 1 entailed, amongst other procedures, an explanation of the study and associated procedures to both the potential participant and his/her parent or guardian. Thereafter, once willingness to participate in the study was expressed by the potential participant and all study-related questions were adequately attended to, informed consent to participate in the study was obtained from the participant's parent or guardian and assent was obtained from the participant. This was followed by a screening assessment which included a structured diagnostic interview to assess for current and lifetime psychiatric disorders, the completion of a demographic questionnaire as well as the completion of various self-report measures. The structured diagnostic interview was conducted in either English or Afrikaans and the demographic questionnaire and self-report measures were available in English, Afrikaans and Xhosa. Participants also underwent a brief physical examination, conducted by a research doctor based in the Department of Psychiatry, Stellenbosch University. In addition, a blood sample was obtained from consenting participants so as to examine gene variants in the serotonin

transporter and BDNF genes. Venous blood was drawn by a research nurse based in the Department of Psychiatry, Stellenbosch University. In addition, the research nurse collected data associated with participants' height, weight, blood pressure, pulse rate, and pregnancy status in consenting female participants. In addition to the above, an eye test (i.e. H.R.R. Pseudoisochromatic Plates), to screen for defective colour vision, was administered to each participant. All blood samples were safely stored at the MAGIC laboratory based at the Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University.

At the second visit, participants underwent a neuropsychological assessment so as to determine participants' IQ, executive functioning performance, visual and verbal memory and learning performance, amongst other cognitive domains. The neuropsychological evaluation was conducted in either English or Afrikaans. The neuropsychological assessment took approximately 2 to 2.5 hours to complete, per participant. Half-way through the neuropsychological assessment, participants were afforded a break period of approximately half an hour.

At the third visit, MRI procedures and precautions were explained to each participant. In addition, participants underwent preparatory training in both functional MRI tasks and were also required to complete a pre- and post-imaging state anxiety questionnaire. The imaging assessment, including the preparatory training and completion of state anxiety questionnaires, took approximately 1.5 to 2 hours to complete, per participant. See Figure 1 detailing the three study visits.

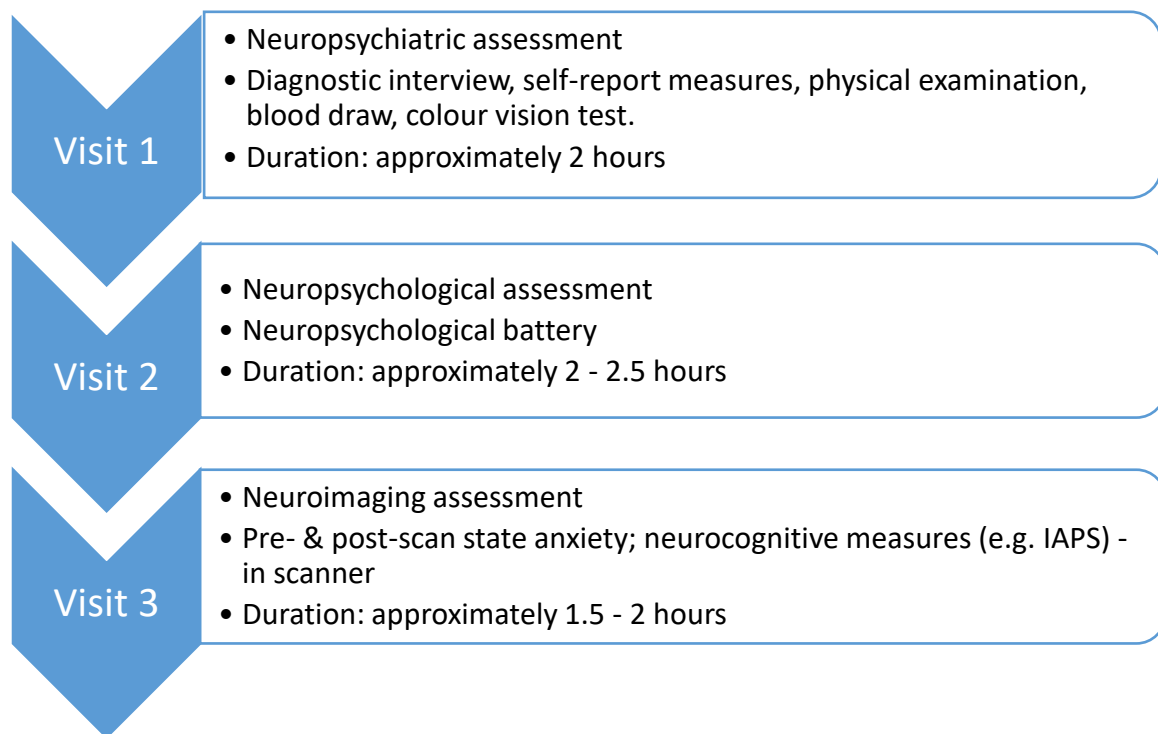


Figure 1 illustrates the three study visits of the second tier of the research as well as the approximate duration of each of the visits.

3.2.4 Study instruments: Tier 1

All Tier 1 study instruments were self-report measures.

(i) Demographic questionnaire

Participants completed a demographic questionnaire which enquired about the following: date of birth; age; ethnicity; current grade at school; parents' marital status; current household composition; current cigarette smoking status and current alcohol and dagga use status; whether they had ever taken medication for stress, anxiety or depression; whether they had ever consulted with a doctor, nurse, counselor or psychiatrist for anxiety problems; and whether they were ever diagnosed with an anxiety disorder, and if so, which anxiety disorder.

(ii) The Childhood Anxiety Sensitivity Index (CASI)

The Childhood Anxiety Sensitivity Index (Silverman, Fleisig, Rabian, & Peterson, 1991) is an 18-item self-report questionnaire, modified from the 16-item Anxiety Sensitivity Index (ASI), commonly used in adult samples (Reiss et al., 1986). The CASI was designed for use with school-age children and adolescents, with a few of the original ASI items being modified to make the items more appropriate and understandable for children and adolescents (Silverman et al., 1991). For example, one of the items from the ASI, “It scares me when I am nauseous”, was adapted to “It scares me when I feel like I am going to throw up” (Silverman et al., 1991). The CASI measures the fear of anxiety symptoms on a 3-point Likert scale [i.e. ‘none’ (1), ‘some’ (2), or ‘a lot’ (3)] by asking participants to rate the extent to which they believe the experience of anxiety will result in negative consequences, comprising physical, psychological and social concerns. The CASI yields a total score by summing the 18 items, and has a range of 18 to 54, with higher scores reflecting higher levels of AS. Silverman et al. (1991) reported good internal consistency ($\alpha = 0.87$) and acceptable test-retest reliability ($r = 0.76$ and 0.79 , respectively) for the CASI in their sample of non-clinical and clinical, primarily Caucasian, children and adolescents. In the current study, the CASI had good internal consistency ($\alpha=0.81$).

Please see Appendix A3: Martin, L., Kidd, M., & Seedat, S. (2016). Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African sample. Published in *Frontiers in Psychology*, 6, 1-10.

(iii) The State-Trait Anxiety Inventory (STAI)

The State-Trait Anxiety Inventory is a 40-item self-report questionnaire consisting of 2 subscales containing 20 items each, with the subscales respectively assessing the presence and severity of current anxiety symptoms (i.e. state anxiety) and the predisposition to be anxious (i.e. trait anxiety) (Julian, 2011; Spielberger et al., 1983). For each of the subscales, items are rated on a 4-point Likert scale. For the trait anxiety subscale (T-Anxiety), responses to items are as follows: ‘almost never’ (1), ‘sometimes’ (2), ‘often’ (3), and ‘almost always’ (4). For the state anxiety subscale (S-Anxiety), responses are as follows: ‘not at all’ (1), ‘somewhat’ (2), ‘moderately so’ (3) and ‘very much so’ (4). Scores for each of the two sections can range between 20 and 80, with higher scores reflecting higher levels of state and trait anxiety

(Spielberger et al., 1983). Test-retest stability coefficients for the T-Anxiety subscale have been found to be relatively high (i.e. ranging from 0.73 to 0.86) for high school and college students, however, stability coefficients for the S-Anxiety subscale were found to be relatively low (i.e. median $r = 0.33$) (Spielberger & Reheiser, 2009), reflecting the S-Anxiety's ability to detect temporary states (Julian, 2011). Good internal consistency has been determined for both the T-Anxiety subscale ($\alpha = 0.90$) and the S-Anxiety subscale ($\alpha = 0.86$ or higher) in large samples of secondary school and college students, adults, and military recruits (Spielberger & Reheiser, 2009). The STAI, as a screening instrument, has been shown to be an adequate measure to predict adolescent anxiety disorders (Hishinuma et al., 2001). The STAI has been utilized in South African samples, for example, in pregnant women (Roos et al., 2012), among clinical and counselling psychologists (Jordaan, Spangenberg, Watson, & Fouche, 2007), in spouses of patients either receiving psychiatric outpatient or inpatient treatment (Spangenberg & Theron, 1999), and in school-attending youth (Martin, Viljoen, Kidd, & Seedat, 2014). In the current study, the STAI trait version had relatively poor internal consistency ($\alpha=0.62$). Additional information relating to the psychometric properties of the STAI trait version in a South African adolescent population is not available.

(iv) The Childhood Trauma Questionnaire – Short Form (CTQ-SF)

The Childhood Trauma Questionnaire – Short Form (CTQ-SF) was derived from the original CTQ, a 70-item self-report inventory that was originally developed to provide both a reliable and valid retrospective measure of a wide range of traumatic childhood experiences (Bernstein et al., 1994). The CTQ was validated in a sample of adult substance abusers and demonstrated sound test-retest reliability, convergent and discriminant validity (Bernstein et al., 1994; Fink, Bernstein, Handelsman, Foote, & Lovejoy, 1995).

The CTQ-SF is a brief, 28-item retrospective self-report measure of the frequency of abuse and neglect experienced prior to age 18 years (i.e. during childhood and adolescence) (Bernstein et al., 2003). It was developed to provide a valid screening instrument for maltreatment histories in both clinical and non-clinical samples (Bernstein et al., 2003) and was validated in four samples, comprising adult substance-dependent, treatment-seeking patients; adolescent psychiatric inpatients; adult substance abusing individuals in the community; and a normative community sample of adults (Bernstein et al., 2003). Measurement invariance of the CTQ-SF was determined across the samples. High internal consistency for the full scale was

demonstrated ($\alpha = .95$) and good criterion-related validity was determined in a subsample of adolescent participants (Bernstein et al., 2003).

The CTQ-SF consists of 5 subscales, each consisting of five items, that assess emotional, physical, and sexual abuse, and emotional and physical neglect, respectively (Bernstein et al., 2003). In addition, a 3-item Minimization/Denial validity scale, developed to detect the underreporting of maltreatment, is included in the CTQ-SF (Bernstein et al., 2003). That said, there is evidence to suggest that the Minimization/Denial scale may not function as a response bias index (MacDonald, Thomas, MacDonald, & Sciolla, 2014), and thus the Minimization/Denial scale was not reported on in this dissertation. Item responses are measured with a Likert scale ranging from 1 ('never true') to 2 ('very often true'). The CTQ-SF yields a total score that can range from 25 to 125, with higher scores reflecting more severe levels of abuse or neglect. Subscale scores can be calculated by summing the relevant items reflective of the various abuse and neglect categories, with each of the 5 subscale scores ranging from 5 to 25.

The CTQ-SF has been utilized in a number of studies in South Africa, including, amongst others, the following samples: school attending adolescents (Suliman et al., 2009) and those with alcohol use disorder (Brooks et al., 2014), adult females (Goedecke, Forbes, & Stein, 2013), and adult psychiatric outpatients (Hemmings et al., 2013; Lochner et al., 2010). Previous assessment of the CTQ-SF in large samples of secondary school students (i.e. Black, mixed race, and Caucasian adolescents) in Cape Town, South Africa, has demonstrated that the CTQ-SF has good internal consistency ($\alpha = 0.74$) (Fincham, Altes, Stein, & Seedat, 2009; Suliman et al., 2009). In the current study, the CTQ-SF had good internal consistency ($\alpha = 0.86$). Additional information relating to the psychometric properties of the CTQ-SF in a South African adolescent population is not available.

For the purposes of the current study, we enquired about maltreatment experienced prior to age 12 years.

(v) The Life Events Timeline

The Life Events Timeline requires participants to subjectively plot, on a timeline, the age at which major life events occurred.

(vi) The Center for Epidemiological Studies Depression Scale for Children (CES-DC)

The CES-DC is a 20-item self-report questionnaire, modified from the 20-item Center for Epidemiological Studies Depression Scale (CES-D) (Faulstich, Carey, Ruggiero, Enyart, & Gresham, 1986; Radloff, 1977; Weissman, Orvaschel, & Padian, 1980). The CES-D was developed as a brief self-report scale to measure current levels of depressive symptomatology in general population surveys (Radloff, 1977). The CES-DC was developed to assess the severity of depressive symptoms in both children and adolescents, with some CES-D items being modified to make the items more suitable, relevant and understandable for youths (Faulstich et al., 1986; Weissman et al., 1980). For example, one of the items from the CES-D, “I felt lonely”, was modified to “I felt lonely, like I didn’t have any friends”. The CES-DC measures past-week depression symptoms and severity on a 4-point Likert scale ranging from 0 (‘not at all’) to 3 (‘a lot’) (Faulstich et al., 1986) by asking participants to indicate ‘how much’ they have felt a certain way during the past week. The CES-DC yields a total score by summing the 20 items and has a range of 0 to 60, with higher scores reflecting higher levels of past-week depressive symptomatology.

The psychometric properties of the CES-DC were evaluated in a sample of children and adolescents, inpatients at psychiatric facilities (Faulstich et al., 1986). Faulstich and colleagues (1986) reported good internal consistency ($\alpha = 0.84$) and relatively low two-week test-retest reliability ($r = 0.51$) for the total sample, however, good test-retest reliability was established in the adolescent sample ($r = 0.69$). A moderate correlation of 0.44 was established between scores on the CES-DC and the Children’s Depression Inventory (CDI) for the total sample, however, concurrent validity in the adolescent sample was adequate ($r = 0.61$) (Faulstich et al., 1986). The CES-DC, in both its original form and adapted versions, has previously been used in South African samples, for example, in healthy secondary school students (Martin et al., 2014) and in AIDS-orphaned and non-orphaned school attenders (Onuoha & Munakata, 2010). The psychometric properties of the CES-DC have been evaluated in a sample of Black undergraduate students in South Africa, with results associated with the scale’s reliability, validity, and factor structure being consistent with previous findings (Pretorius, 1991). In the current study, the CES-DC had good internal consistency ($\alpha=0.87$). Additional information relating to the psychometric properties of the CES-DC in a South African adolescent population is not available.

(vii) The Alcohol Use Disorders Identification Test (AUDIT)

The AUDIT is a 10-item screening instrument developed to screen effectively for a broad range of problem drinking behaviours, including both hazardous and harmful alcohol consumption (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The AUDIT taps into the domains of alcohol consumption, drinking behaviour, and alcohol-related problems (i.e. both past year and lifetime) (Saunders et al., 1993). The AUDIT was developed in a large sample of primary health care attendees in six countries (i.e. Australia, Kenya, Bulgaria, Mexico, Norway and the USA). These attendees comprised participants that were categorized as ‘non-drinkers’, ‘drinkers’, and ‘alcoholics’ (Saunders et al., 1993), with the information provided from those classed as ‘drinkers’ used to select appropriate items for inclusion in the AUDIT. The remaining two groups were used to validate the AUDIT (Saunders et al., 1993). Since the development of the AUDIT, numerous studies have determined that the AUDIT has sound psychometric properties, for example, test-retest reliability and internal consistency (Reinert & Allen, 2007). A median reliability coefficient of 0.83, with a range of 0.75 to 0.97 was determined in an assessment of studies that utilized the AUDIT (Reinert & Allen, 2007). There is therefore support for the utility of the AUDIT in identifying problematic drinking behaviours in a range of contexts and cultures (Meneses-Gaya, Zuardi, Loureiro, & Crippa, 2009).

Of the 10 items comprising the AUDIT, three measure alcohol consumption or intake, three measure drinking behaviour, two measure adverse reactions, and two measure alcohol-related problems. Each of the items are scored from ‘0’ to ‘4’, with a total score for the AUDIT ranging from 0 to 40 (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001; Saunders et al., 1993). Responses are measured with a Likert-type scale and range from ‘never’ and ‘less than monthly’ to ‘daily’ (Babor et al., 2001; Saunders et al., 1993). In a large sample of male and female adolescents receiving healthcare at a clinic, an optimal cut-point on the AUDIT of 2, with a sensitivity and specificity of 0.88 and 0.81, respectively, was determined as an indicator of alcohol problem use (Knight, Sherritt, Harris, Gates, & Chang, 2003). A cut-point of 3 was found to be optimal for identifying those with abuse or dependence (Knight et al., 2003).

The AUDIT has been used in a number of South African studies, including, amongst others, in pregnant females residing in townships in Cape Town (O’Connor et al., 2011), in young adult males and females residing in the Cape Flats (Adams, Savahl, Isaacs, & Carels, 2013), in urban high school students (Betancourt & Herrera, 2014), and in students attending informal settlement schools (Kaufman et al., 2014). Previous assessment of the AUDIT in a sample of

Black secondary school attending adolescents has demonstrated that the AUDIT has good internal consistency (i.e. $\alpha = 0.88$ for girls, and $\alpha = 0.71$ for boys) (Gevers, Jewkes, & Mathews, 2013). In the current study, the AUDIT had good internal consistency ($\alpha = 0.87$). Additional information relating to the psychometric properties of the AUDIT in a South African adolescent population is not available.

(viii) The Drug Use Disorders Identification Test (DUDIT)

The DUDIT is an 11-item screening instrument developed to effectively screen for and identify drug use patterns and current drug-related problems in individuals, and to act as a corresponding measure to the AUDIT (Berman, Bergman, Palmstierna, & Schlyter, 2005). The DUDIT was developed in a sample of adult drug users from prison, probation and inpatient detoxification units, as well as in a large general Swedish population sample (Berman et al., 2005). A recent review of 18 publication that reported on the psychometric properties of the DUDIT found generally satisfactory validity and reliability indices, providing support for the DUDIT's utility in both clinical and research settings (Hildebrand, 2015).

Responses for the DUDIT items are measured with a Likert-type scale and range from 0 ('never') to 4 ('daily or almost every day') for the first nine items, and for the last two items, responses are 0 ('no'), 2 ('yes, but not over the past year'), and 4 ('yes, over the past year') (Berman et al., 2005). The DUDIT yields a total score ranging from 0 to 44, with higher scores indicating higher levels of drug-related problems (Berman et al., 2005).

The DUDIT has been used in a number of South African studies, including, amongst others, in secondary school students (Martin et al., 2014), in adolescent school-attenders from low-income communities (Hendricks, Savahl, & Florence, 2015), in undergraduate university students (De Jager, Suliman, & Seedat, 2014), and in HIV-positive patients attending a health clinic (Kader, Seedat, Koch, & Parry, 2012). In the current study, the DUDIT had good internal consistency ($\alpha = 0.89$). Additional information relating to the psychometric properties of the DUDIT in a South African adolescent population is not available.

(ix) The Connor-Davidson Resilience Scale (CD-RISC)

The CD-RISC is a brief 25-item self-report questionnaire, developed to provide a well-validated and reliable measure of resilience (i.e. successful stress-coping ability) in both clinical and non-clinical populations (Connor & Davidson, 2003).

The psychometric properties of the CD-RISC were determined in a diverse group of adults (i.e. a general population sample, primary care outpatients, psychiatric outpatients in private practice, individuals in a study of generalized anxiety disorder, and individuals in two clinical trials of PTSD) (Connor & Davidson, 2003). Good internal consistency was determined for the full scale in the general population sample ($\alpha = 0.89$), with item-total correlations ranging from 0.30 to 0.70 (Connor & Davidson, 2003). Good test-retest reliability was determined (i.e. intraclass $r = 0.87$) in participants in the clinical trials of GAD and PTSD (Connor & Davidson, 2003). In addition, there was evidence for both convergent and discriminant validity, with, for example, CD-RISC scores correlating positively and significantly with a measure of hardiness ($r = 0.83, p < 0.0001$) and no significant correlation being determined with a sexual experiences scale ($r = -.34, p = 0.11$) (Connor & Davidson, 2003). A review of resilience measurement scales found that of the fifteen measures that were reviewed, the CD-RISC was one of three that had the most favourable psychometric characteristics (Windle, Bennett, & Noyes, 2011).

Responses to the CD-RISC are measured on a 5-point Likert-type scale, with responses ranging from 0 ('not true at all') to 4 ('true nearly all of the time'), based on how the individual has felt over the past month. The CD-RISC yields a total score ranging from 0 to 100, with higher scores indicating higher levels of resilience (Connor & Davidson, 2003).

The CD-RISC has been used in a number of South African studies, including, samples of secondary school students (Bruwer, Emsley, Kidd, Lochner, & Seedat, 2008; Martin et al., 2014), adolescent and adult female rape survivors (van der Walt, Suliman, Martin, Lammers, & Seedat, 2014), and HIV-positive women with early life adversity (Spies & Seedat, 2014). An examination of the factor structure of the CD-RISC in a sample of Black, mixed race, and Caucasian adolescents in South Africa indicated either a three-factor or a two-factor structure in the sample. In addition, excellent internal consistency was determined ($\alpha=0.93$) (Jørgensen & Seedat, 2008). In the current study, the CD-RISC had excellent internal consistency

($\alpha=0.92$). Additional information relating to the psychometric properties of the CD-RISC in a South African adolescent population is not available.

(x) The Adolescent Coping Orientation for Problem Experiences (A-COPE)

The A-COPE is a 54-item self-report measure developed to identify coping behaviours and styles that adolescents consider helpful in managing problems or difficult situations (Patterson & McCubbin, 1987).

The A-COPE was constructed, developed and validated in three separate samples of adolescents (i.e. secondary school students, primary and secondary school students, and adolescents from families enrolled in a health maintenance organization in the United States) (Patterson & McCubbin, 1987). Fair to good internal consistency of the subscales was determined, with Cronbach's alphas ranging from 0.5 to 0.76. Concurrent validity of the A-COPE was assessed by examining correlations between coping patterns and drug and alcohol use. Significant correlations were determined for many of these relationships for both males and females. For example, for males, cigarette, beer, alcohol and marijuana use was found to be significantly and positively associated with the coping patterns of 'ventilating feelings' and 'investing in close friendships' (Patterson & McCubbin, 1987).

Responses to the A-COPE are measured on a 5-point Likert-type scale, with responses ranging from 1 ('never') to 5 ('most of the time') (Patterson & McCubbin, 1987). The A-COPE yields a total score, which provides an overall measure of coping, with a total score that can range from 54 to 270. Higher A-COPE scores indicate higher levels of coping behaviour.

The A-COPE has previously been used in samples of public secondary school students in South Africa (Martin et al., 2014; Moodley et al., 2012). The assessment of the A-COPE in English and Afrikaans speaking adolescent school students in South Africa demonstrated that the internal consistency of the A-COPE subscales ranged from fair to good (i.e. $\alpha=0.50-0.75$) (Moodley et al., 2012). In the current study, the A-COPE had good internal consistency ($\alpha=0.84$). Additional information relating to the psychometric properties of the A-COPE in a South African adolescent population is not available.

3.2.5 Study instruments: Tier 2

3.2.5.1 Structured diagnostic interview

The Mini-International Neuropsychiatric Interview-Kid for children and adolescents (MINI-KID)

The MINI-KID (Sheehan et al., 2010) is a brief, accurate and reliable structured clinical diagnostic interview that was designed to assess the presence of 24 DSM-IV and ICD-10 psychiatric disorders and suicidality in children and adolescents aged 6 to 17 years of age (Sheehan et al., 2010). The MINI-KID, which takes about half an hour to administer, can be used in both clinical and research settings (Sheehan et al., 2010) and has the same structure and format of the MINI (i.e. the adult version of the clinical diagnostic interview) that was validated against the Structured Clinical Interview for DSM-III-R (Sheehan et al., 1998) and the Composite International Diagnostic Interview (Lecrubier et al., 1997). The MINI-KID can be administered to the child or adolescent either with or without a parent present (Sheehan et al., 2010).

The reliability and validity of the MINI-KID was assessed in a sample of 226 children and adolescents (i.e. outpatients from a child and adolescent outpatient program and community controls recruited from a community church organization) with a mean age of 12.8 years ($SD = 3.5$) (Sheehan et al., 2010). Excellent interrater and test-retest reliability was determined for all individual MINI-KID disorders, besides dysthymia. Furthermore, substantial to excellent concordance between MINI-KID to Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was found for syndromal diagnoses of any mood, anxiety, substance use, ADHD or behavioural disorder and any eating disorder. Substantial sensitivity and specificity was determined (Sheehan et al., 2010).

3.2.5.2 Self-report instruments

(i) Demographic questionnaire

As in Tier 1, Participants completed a demographic questionnaire which enquired about the following: date of birth; age; ethnicity; current grade at school; parents' marital status; current

household composition; current cigarette smoking and current alcohol and marijuana use status; whether they had ever taken medication for stress, anxiety or depression; whether they had ever consulted with a doctor, nurse, counselor or psychiatrist for anxiety problems; and whether they were ever diagnosed with an anxiety disorder.

In addition to the above, a socio-economic status scale was administered to each participant. This scale required participants to indicate whether or not they had access to basic household necessities in the home in which they resided, for example, whether they had a tap with hot running water in the home, whether they had a stove, fridge, television, and flush toilet in their home, whether they slept on their own bed, had enough food in their homes for two meals a day, whether they had access to electricity or gas in their home, and whether they were adequately clothed. Responses to these questions were dichotomous, namely, ‘yes’ or ‘no’, coded ‘1’ for ‘yes’ and ‘0’ for ‘no’, with a greater score reflective of a higher socio-economic status. This scale has previously been used in a sample of South African youths (Gregorowski et al., 2016).

(ii) The Childhood Anxiety Sensitivity Index (CASI)

See 3.2.4 (ii)

In the current study, the CASI had good internal consistency ($\alpha=0.86$).

(iii) The State-Trait Anxiety Inventory (STAI)

See 3.2.4 (iii)

In the current study, the STAIT trait version had good internal consistency ($\alpha=0.83$).

(iv) The Children’s Depression Inventory (CDI)

The CDI (Kovacs, 1985) is a 27-item self-report scale, based on the Beck Depression Inventory for adults (Beck, Ward, & Mendelson, 1961). It was developed so as to provide an economical and easily administered tool to quantify the severity of depressive symptoms in children and adolescents in clinical research settings (Kovacs, 1985). The CDI measures aspects of depression, such as negative mood, isolation and social avoidance, low self-esteem and self-dislike, and anhedonia (Kovacs, 1985, 1992).

The reliability of the CDI was determined in two samples of youth (i.e. youths aged 8 to 13 years referred to a child guidance center and children diagnosed with insulin-dependent diabetes mellitus that were admitted to a pediatric metabolic unit) (Kovacs, 1985). Good internal consistency was determined and test retest reliability was found to be acceptable (Kovacs, 1985). A study in three independent samples from public schools provided further evidence for the reliability of the CDI (Smucker, Craighead, Craighead, & Green, 1986). Validity of the CDI was determined by Kovacs (1985), with significant correlations between the CDI and measures of anxiety and self-esteem being determined.

The CDI items are rated on a 3-point Likert-type scale ranging from 0 to 2. Participants are asked to choose, for each item, one sentence from three possible sentences that describe them best for the past two weeks, for example, 'I am sad once in a while', or 'I am sad many times' or 'I am sad all the time'. The CDI produces a total score ranging from 0 to 54, with higher scores indicating increased severity (Kovacs, 1985).

The CDI has been used in a number of South African studies, including samples of adolescent primary and secondary school students (Bach & Louw, 2010; Rawatlal, Kliwer, & Pillay, 2015), and children of HIV-positive and HIV-negative mothers (Sipsma et al., 2013). The assessment of the CDI in a sample of adolescents from public schools in KwaZulu Natal, South Africa, determined that the CDI had good internal consistency ($\alpha=0.86$) (Rawatlal et al., 2015). In the current study, the CDI had good internal consistency ($\alpha=0.83$). Additional information relating to the psychometric properties of the CDI in a South African adolescent population is not available.

(v) The Adolescent Drinking Inventory (ADI)

The ADI (Harrell, Sowder, & Kapsak, 1988) is a brief 24-item alcohol screening instrument developed for use by clinicians and counselors to aid in determining whether an adolescent may have alcohol-related drinking problems and whether they should be referred for further evaluation (Harrell & Wirtz, 1989; McPherson & Hersch, 2000). Problem drinking is conceptualized by the ADI as it relates to symptoms associated with alcohol-related dysfunction in a number of domains (i.e. drinking-related loss of control; social indicators such as problems with friends, family, the law, and school authorities; psychological indicators such

as drinking alcohol for relaxation or to alter mood; and physical indicators such as increased tolerance and memory difficulties (Harrell & Wirtz, 1989; McPherson & Hersch, 2000).

Excellent internal consistency (i.e. 0.96) and test-retest reliability (i.e. $r = 0.78$) has been determined. In addition, high sensitivity and specificity have been determined, with the ADI correctly identifying almost 90% of adolescents who had significant or moderate drinking problems, and correctly classifying over 80% of those with no or minimal drinking problems (Harrell & Wirtz, 1989; McPherson & Hersch, 2000). There is also evidence for satisfactory discriminant validity (McPherson & Hersch, 2000).

The ADI produces a total score that can range from 0 to 62, by summing the item scores for the 24 items. A cut-off score of 16 has been established as indicating a need for further evaluation and is suggestive of alcohol abuse (Maag & Irvin, 2005). In the current study, the ADI had good internal consistency ($\alpha=0.89$). Additional information relating to the psychometric properties of the ADI in a South African adolescent population is not available.

(vi) The Multidimensional Anxiety Scale for Children (MASC)

The MASC (March, 1997) is a 39-item self-report measure of anxiety symptoms and anxiety dimensions in children (March, 1997). The MASC was developed to provide both a practical and efficient screening instrument for measuring anxiety in children and adolescents aged 8 to 19 years (March, 1997).

The psychometric properties of the MASC were assessed in a large sample of child and adolescent primary and secondary school students (March, 1997). Studies that have utilized the MASC have reported adequate to good internal reliability in the scale overall as well as the four subscales (Baldwin & Dadds, 2007; Ivarsson, 2006; March, 1997; Ndeti et al., 2008; Wei et al., 2014). High test-retest reliability for the whole scale and the subscales has been determined (March, Sullivan, & Parker, 1999; March, 1997), as has adequate factorial, discriminant and convergent validity (Anderson, Jordan, Smith, & Inderbitzen-Nolan, 2009; Baldwin & Dadds, 2007; Ivarsson, 2006; March, 1997; Ndeti et al., 2008; Rynn et al., 2006; Wei et al., 2014).

The MASC items are rated on a 4-point Likert-type scale ranging from 0 ('never true about me') to 3 ('often true about me') with participants being required to rate the items in terms of their own experience (March, 1997). The MASC provides a total score and subscale scores for various anxiety dimensions (i.e. physical symptoms, harm avoidance, social anxiety, separation anxiety/panic), with higher scores indicating increased emotional problems (March, 1997).

The MASC has been used in a number of South African studies, such as in samples of secondary school students (Brink, Louw, Grimmer, & Jordaan, 2015; Fincham et al., 2008; Suliman et al., 2009), and adolescent methamphetamine users, cannabis users, and controls (Cuzen, Koopowitz, Ferrett, Stein, & Yurgelun-Todd, 2015). The examination of the factor structure of the MASC in Black, mixed race, and Caucasian adolescent school students in South Africa determined a four-factor structure consistent with previous findings in adolescent samples (Fincham et al., 2008). In addition, the previous study determined that the MASC demonstrated excellent internal consistency ($\alpha=0.90$) (Fincham et al., 2008). In the current study, the MASC had good internal consistency ($\alpha=0.86$). Additional information relating to the psychometric properties of the MASC in a South African adolescent population is not available.

3.2.5.3 Neuropsychological test battery

The domains assessed and tests used to assess each domain are displayed in Table 3.

Table 3

Neuropsychological tests used to assess neuropsychological domains.

Neuropsychological domain	Neuropsychological test
Cognitive functioning	MMSE
IQ	WASI
Memory and learning	
Verbal memory and learning	RAVLT
Visual memory and learning	ROCF
	WMS-R
Executive functioning	
Cognitive flexibility	TMT-B
Verbal fluency	COWAT
Planning	TOL
Verbal working memory	SSAIS-R Digit span
Visuo-spatial skills	
Visuo-spatial constructional ability	ROCF
Visuo-spatial skills and non-verbal concept formation	SSAIS-R Block design
Visual perception and conceptual abilities	SSAIS-R Missing parts
Psychomotor speed	TMT-A
	GPT

(i) The Mini-Mental State Examination (MMSE)

The MMSE is a brief, untimed, 11-item screen of the cognitive aspects of mental functioning, and takes up to 10 minutes to administer (Folstein, Folstein, & McHugh, 1975). It is a useful

measure to screen for cognitive functioning and also assesses change in cognitive functioning over time (Strauss, Sherman, & Spreen, 2006). MMSE items are grouped into seven categories representative of various cognitive domains (i.e. orientation to time and place; registration and recall of words; memory, attention and calculation; language and visual construction) (Folstein et al., 1975; Strauss et al., 2006; Tombaugh & McIntyre, 1992).

The validity and reliability of the MMSE were evaluated in a sample of elderly patients with various clinical conditions (e.g. dementia, affective disorders, mania, schizophrenia and personality disorders) and in a sample of normal elderly participants. The MMSE was shown to be a valid and reliable test of cognitive function. The MMSE was found to have good discriminant validity, concurrent validity, and excellent test-retest reliability (Folstein et al., 1975). An earlier review of the MMSE in both community and clinical samples has provided evidence for the utility of the MMSE (Tombaugh & McIntyre, 1992).

The maximum score on the MMSE is 30 (Folstein et al., 1975; Strauss et al., 2006; Tombaugh & McIntyre, 1992). Scores between 24 and 30 indicate no cognitive impairment, scores between 18 and 23 indicate mild cognitive impairment, and those between 0 and 17 are indicative of severe cognitive impairment (Tombaugh & McIntyre, 1992).

The MMSE was originally designed to screen mental impairment in the elderly and is currently also used in child and adolescent populations (e.g. Tsantali, Economidis, Rigopoulou, & Porpodas, 2012). The MMSE has previously been administered in community samples of children (Rubial-Alvarez et al., 2007), adolescents and young adults (Feijó, Saueressig, Salazar, & Chaves, 1997), as well as in adolescent psychiatric outpatients (Cohen et al., 2000; Wagner et al., 2006). In a sample of children aged between 4 and 12 years, MMSE scores were found to correlate significantly with chronologic and mental age and verbal intelligence scores, with children aged from 6 years having an average score of 24 and above (Rubial-Alvarez et al., 2007).

(ii) The Edinburgh Handedness Inventory (EHI)

The EHI was developed to provide a brief quantitative measure of hand laterality (Oldfield, 1971). It is a self-report measure in which participants respond to questions regarding their preference to use either their left or right hand on 10 manual tasks (e.g. writing, throwing,

cutting with scissors, brushing teeth, using a spoon) (Hardie & Wright, 2014). Responses to items are ‘always left’, ‘usually left’, ‘no preference’, ‘always right’, and ‘usually right’. The EHI provides a measure of handedness by converting responses to items into a laterality quotient that can range from -100 for complete left-handedness to +100 for complete right-handedness (Hardie & Wright, 2014).

The EHI has been widely used to determine handedness in samples of youth, for example, trauma-exposed children and adolescents with posttraumatic stress symptoms and control subjects (Carrion, Garrett, Menon, Weems, & Reiss, 2008) and healthy youths and youths with major depressive disorder (Ladouceur et al., 2012).

(iii) The Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT (Rey, 1941) is a brief pencil and paper measure that assesses verbal memory, namely, immediate memory span; new learning, influence of interference, and recognition memory. The RAVLT is a useful test to determine memory system deficits (Lezak, Howieson, & Loring, 2004).

In the current study, the RAVLT AB test format was employed. This format contains five presentations with recall of a fixed 15 monosyllabic-word list that is read aloud to the participant, with a one second interval between each word, and with the order of presentation of words remaining fixed across presentations. Each presentation or trial is followed by a free recall test A (i.e. Trials I-V), in which participants are to recall, in any order, as many words as they can. Before each trial, instructions are repeated. An interference or distractor list of 15 words, List B, is presented, once Trial V has been completed, followed by a free recall test. Thereafter, delayed recall of the first list, List A, is tested, namely, Trial VI, in the absence of the list of words being repeated by the examiner. After approximately a half hour delay period, participants are required to recall the words from List A (Trial VII). Assessment of recognition of words follows, with 50 words, including the 30 words from Lists A and B, and 20 distractor words (i.e. phenomenically similar or semantically associated words) being presented to participants to identify words from List A (Delaney, Prevey, Cramer, & Mattson, 1992; Lezak et al., 2004; Uchiyama et al., 1995; Van der Elst, van Boxtel, van Breukelen, & Jolles, 2005).

Good test-retest reliability has been determined in normal controls (Lezak et al., 2004), and good internal consistency has been determined in a normative sample of school children (Van Den Burg & Kingma, 1999). Furthermore, the learning measures of the RAVLT have been shown to correlate significantly with other measures of learning (Lezak et al., 2004).

Certain demographic variables have been found to influence performance on the RAVLT, for example age, gender, ethnicity, socio-economic status, education and intellectual ability (Savage & Gouvier, 1992; Uchiyama et al., 1995; Vakil, Greenstein, & Blachstein, 2010; Van Den Burg & Kingma, 1999). The RAVLT has previously been administered in samples of youth, including trauma-exposed youth with and without PTSD (Schoeman, Carey, & Seedat, 2009), youth with a diagnosis of major depressive disorder (Baune, Czira, Smith, Mitchell, & Sinnamon, 2012), and public school attending children and adolescents (Vakil et al., 2010).

(iv) The Rey-Osterreith Complex Figure Test (ROCF)

The ROCF (Rey, 1941) is a widely used test to assess visual-spatial constructional ability and visual memory (Camara, Nathan, & Puente, 2000; Strauss et al., 2006). The ROCF comprises three test conditions, namely, copy, immediate recall and delayed recall. It requires participants to firstly copy a complex figure (i.e. copy task) consisting of a two-dimensional line drawing containing 18 details (Mitrushina, Boone, & D'Elia, 1999), and immediately after completion of the copy task, participants are required to recall, without prior warning, the complex figure (i.e. immediate recall task). After approximately 30 to 45 minutes of the immediate recall task, participants are required to recall, again without prior warning, the complex figure (i.e. delayed recall task) (Strauss et al., 2006). Scores are obtained by allocating points for how accurately the components of the complex figure have been reproduced in terms of accuracy, distortion and location (Shin, Park, Park, Seol, & Kwon, 2006; Shuttleworth-Edwards, Kock, & Radloff, 2015; Strauss et al., 2006).

The copy task accesses attention, concentration and visuo-constructional ability and requires spatial organizational ability (i.e. visual-motor function and planning, organizational abilities) which aid in executive skills (Shin et al., 2006; Shuttleworth-Edwards et al., 2015; Strauss et al., 2006). The immediate recall task accesses attention, visuo-constructional ability and executive functioning and requires short term visual memory to complete effectively (Shin et al., 2006; Shuttleworth-Edwards et al., 2015; Strauss et al., 2006). The delayed recall task

assesses whether long term visual memory encoding has occurred (Shuttleworth-Edwards et al., 2015; Strauss et al., 2006).

Good internal, interrater and alternate form reliability have been reported for the ROCF (Loring, Martin, Meador, & Lee, 1990; Shin et al., 2006; Strauss et al., 2006). Some studies have found that certain demographic variables influence performance on the ROCF task, namely, age, gender, education, IQ and ethnicity (Gallagher & Burke, 2007; Luzzi et al., 2011; Mitrushina et al., 1999; Shuttleworth-Edwards et al., 2015; Strauss et al., 2006).

The ROCF has previously been administered in samples of youth, including community samples of adolescents (Beebe, Ris, Brown, & Dietrich, 2004; Poulton & Moffitt, 1995), trauma-exposed youth with and without PTSD (Schoeman et al., 2009), and children and adolescents with learning, emotional and behavioural problems and attention deficit disorders (Smith & Zahka, 2006).

(v) The Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI (Wechsler, 1999) is a brief and reliable measure of intelligence that can be used in clinical, educational, and research settings (The Psychological Corporation, 1999). The WASI was developed as a screening measure to provide a brief assessment of IQ and is based on the assessment of both verbal and nonverbal abilities (Strauss et al., 2006). The WASI can be administered to individuals 6 to 89 years of age (Strauss et al., 2006). In the current study, the WASI two-subtest form was used which consists of the Vocabulary subtest and the Matrix Reasoning subtest and provides a full-scale IQ and estimation of general cognitive functioning (Strauss et al., 2006).

The WASI Vocabulary subtest comprises 42-items. The first 4 items consist of pictures which are displayed individually and the participant is required to name these pictures. The remaining items are both orally and visually (i.e. written form) presented words. The participant is required to provide a verbal definition for each word. Responses are scored from 0 to 2 points according to specified scoring criteria (The Psychological Corporation, 1999). The Matrix Reasoning subtest comprises a series of 35 incomplete gridded patterns which the participant is required to complete by selecting (i.e. either by pointing to or stating) the number associated

with the correct response, from a selection of five possible answers (The Psychological Corporation, 1999).

Reliability coefficients of the subtests have been found to range between 0.87 and 0.92, with moderately higher coefficients being determined for adults relative to children (Strauss et al., 2006). Good interrater and test-retest reliabilities for the WASI have been reported (Strauss et al., 2006) and good convergent validity (Canivez, Konold, Collins, & Wilson, 2009) and construct validity have been determined (Strauss et al., 2006). Furthermore, The WASI manual has reported good discriminant and factorial validities (The Psychological Corporation, 1999). Some studies have found that certain demographic variables influence performance on the WASI, including age and education (Panagiotis, Kasselimis, & Mouzaki, 2011; Strauss et al., 2006).

The WASI has previously been administered in samples of youth, including, a representative sample of school and university students (Abu-Hilal, Al-Baili, Sartawi, Abdel-Fattah, & Al-Qaryouti, 2011), healthy and referred children and adolescents (Canivez et al., 2009; Raggio, Scattone, & May, 2010).

(vi) The Trail Making Test A and B (TMT A and B)

The TMT (Reitan, 1958, 1979) is a brief two-part test (i.e. Part A and Part B), that provides a measure of attention, speed, cognitive flexibility, scanning, and visuo-motor tracking (Lezak et al., 2004; Strauss et al., 2006). The TMT is a timed task and requires approximately 5 to 10 minutes to complete (Strauss et al., 2006). Part A requires the participant to connect in ascending order, 25 encircled numbers (i.e. from 1 to 25) randomly organized on a page, as quickly as possible, by making pencil lines to connect the numbers (Lezak et al., 2004; Mitrushina et al., 1999; Strauss et al., 2006). Part A tests participants' visual scanning, numeric sequencing and processing speed. Part B requires the participant to alternate between linking numbers (i.e. 1 to 13) in ascending order and letters in alphabetical order (i.e. from A to L), as quickly as possible, for example, 1-A, 2-B, 3-C (Mitrushina et al., 1999). Part B tests additional cognitive demands including visual-motor and visual-spatial abilities and mental flexibility. Commonly, an individual's score on the TMT is representative of the amount of time taken to complete Part A and Part B, individually.

Reliability coefficients have been reported to vary considerably, with most found to be above 0.60 (Lezak et al., 2004). Test-retest reliabilities have been found to be adequate for Part A and have ranged from adequate to good for Part B (Strauss et al., 2006). Both alternate form and interrater reliability coefficients have been determined as ranging from good to high (Strauss et al., 2006). Validity of the TMT has been established with the TMT correlating significantly with other known measures of speeded processing (Royan, Tombaugh, Rees, & Francis, 2004), visual-motor scanning (Shum, McFarland, & Bain, 1990) and executive control (Kortte, Horner, & Windham, 2002).

Some studies have found that certain demographic variables influence performance on the TMT, including age, education, IQ, gender, and ethnicity (Mitrushina et al., 1999; Strauss et al., 2006).

The TMT has previously been administered in samples of youth, including, children diagnosed with anxiety disorders and ADHD (Yurtbasi et al., 2015); adolescents diagnosed with ADHD (Martel, Nikolas, & Nigg, 2007); anxious-depressed boys and non-anxious, non-depressed boys (Emerson, Mollet, & Harrison, 2005); trauma-exposed youth with and without PTSD (Schoeman et al., 2009) and undergraduate students (Atkinson et al., 2010).

(vii) The Grooved Pegboard Test (GPT)

The GPT provides a measure of eye-hand coordination, fine motor control and psychomotor speed and is commonly used to assess motor impairment (Lezak et al., 2004; Mitrushina et al., 1999). The GPT is considered a cognitive-motor task with performance being dependent on psychomotor speed (Mitrushina et al., 1999). The GPT consists of a small metal board containing a 5 x 5 set of slotted holes, with the slots of each hole being angled in different directions (Lezak et al., 2004). Each peg has a ridge along one side and must be rotated adequately to match the slotted hole prior to being inserted (Lezak et al., 2004; Strauss et al., 2006). The participant is required to insert the metal pegs into the slots in a sequenced fashion (i.e. in a given direction, without skipping any of the slots), as quickly as possible, first with the dominant hand and thereafter with the non-dominant hand, until all the pegs have been placed on the metal board (Strauss et al., 2006). The GPT score is based on time in seconds required to complete placing the metal pegs in all of the grooved slots on the pegboard with each hand separately (Lezak et al., 2004; Strauss et al., 2006). Poorer performance is reflected

in higher scores (Mitrushina et al., 1999). The preferred hand is reportedly not always the faster of the two hands (Strauss et al., 2006).

Reliability of the GPT has been determined, with reliability coefficients for the dominant hand ranging between 0.60 and 0.76, and for the non-dominant hand ranging between 0.68 and 0.78, over a period of 6 months in normal volunteers (Ruff & Parker, 1993). Test-retest reliability estimates for the GPT have been found to be good, ranging from 0.70 to low 0.90s in normal adolescents and adults (Dikmen, Heaton, Grant, & Temkin, 1999). In terms of the validity of the GPT, pegboard time of the dominant hand has been found to correlate moderately with tapping speed and moderate to high associations have been found between the GPT and measures of attention, perceptual speed and non-verbal reasoning (Schear & Sato, 1989; Strauss et al., 2006; Streng, Niederberger, & Seelhorst, 2002; Wang et al., 2011).

Certain demographic variables have been found to influence scores on the GPT, including, age, education, gender, and hand preference (Lezak et al., 2004; Mitrushina et al., 1999; Rosselli, Ardila, Bateman, & Guzmán, 2001; Strauss et al., 2006).

The GPT has previously been administered in samples of youth, including school attending children and adolescents (Ferrett et al., 2014; Mayes, Calhoun, Bixler, & Zimmerman, 2009; Rosselli et al., 2001), adolescents with varying levels of alcohol use (Ferrett, Carey, Thomas, Tapert, & Fein, 2010), and healthy children, adolescents and young adults (Wang et al., 2011).

(viii) The Wechsler Memory Scale-Revised (WMS-R)

The WMS-R is a widely used scale to assess memory function (Lezak et al., 2004) in adolescents and adults (Wechsler, 1987). In the current study, the Visual Reproduction (VR) subtest was employed. The VR subtest is a visual learning and memory test that assesses both immediate and delayed recall for a visual drawing task (Lezak et al., 2004; Wechsler, 1987). The VR task consists of four items that contain abstract line drawings which the participant is required to copy and recall. For the immediate recall task, participants are shown each item individually for 5 seconds and immediately thereafter the participant is required to draw from memory what he/she can remember. The delayed recall task takes place after approximately a half hour delay, and without prior warning to the participant. The participant is required to

draw, once again, from memory, what he/she can remember. An immediate and delayed visual memory score is produced by adding the scores of the 4 reproductions.

Adequate to high reliability coefficients of the subtests and indices have been reported, with stability coefficients ranging from 0.62 to 0.82. Similarly, interrater reliability for subtests have been found to be high (Wechsler, 1987).

Certain demographic variables may influence performance on the WMS-R, including IQ (Tremont, Hoffman, Scott, Adams, & Nadolne, 1997), education, and cultural background (Walker, Batchelor, & Shores, 2009).

Subtests of the WMS-R have previously been administered in samples of youth, such as adolescents diagnosed with ADHD (Quinlan & Brown, 2003) and trauma-exposed youth with and without PTSD (Ahmed, Spottiswoode, Carey, Stein, & Seedat, 2012; Schoeman et al., 2009).

(ix) Senior South African Individual Scale-Revised (SSAIS-R)

The SSAIS-R is an intelligence test, composed of a number of independent tasks that primarily measure verbal and non-verbal mental abilities (van Eeden, 1997). The SSAIS-R is standardized for Afrikaans- and English-speaking students aged from 5 years 0 months to 17 years 11 months (van Eeden, 1997). The measure allows for the calculation of a general intelligence score and individual tests can be scored and analyzed separately (van Eeden, 1997). In the current study, three subtests of the SSAIS-R were employed, namely, Memory for Digits, which constitutes a verbal test; Block Designs and Missing Parts, which both reflect non-verbal tests (van Eeden, 1997).

Memory for Digits consists of both Digits Forward and Digits Backward. In terms of Digits Forward, the examiner reads out a series of digits and the participant is required to repeat the series of digits verbatim, in the same sequence. In terms of Digits Backward, the examiner reads out a series of digits and the participant is required to repeat the series of digits in reversed sequence. This test measures auditory short-term memory for numbers as well as attention and concentration (van Eeden, 1997).

Block Designs consists of 15 items (of which the first three are practice examples) and comprises plastic blocks which are used to copy specific patterns from examples that are presented to the participant (van Eeden, 1997). For items 1 and 2, a model is presented to the participant and for the remaining items, design cards are presented (van Eeden, 1997). This test measures non-verbal concept formation, including perceptual organization, spatial visualization and orientation, and abstract conceptualization (van Eeden, 1997). Logical reasoning is required, as is concentration and visual-motor co-ordination (van Eeden, 1997). Missing Parts consists of 20 pictures, each of which are missing an essential part. The participant is required to indicate, either verbally or by pointing out, what is missing from each of the pictures (van Eeden, 1997). According to van Eeden (1997), this test measures perceptual and conceptual abilities as these play a role in visually recognizing, identifying and understanding familiar objects and situations.

The SSAIS-R was normed in a large sample of English- and Afrikaans-speaking, primary and secondary school students, aged 7 to 16 years (van Eeden, 1997). Excellent reliability coefficients for the full scale were determined and good to excellent reliability coefficients for the above-named tests were determined (van Eeden, 1997). Validity of the SSAIS-R has been determined (van Eeden, 1997; van Eeden & Visser, 1992).

Subtests of the SSAIS-R have previously been administered in samples of youth in South Africa, including trauma-exposed youth with and without PTSD (Schoeman et al., 2009), and primary and secondary school-attending children and adolescents (Cockcroft & Blackburn, 2005; van Eeden & Visser, 1992).

(x) The Controlled Oral Word Association Test (COWAT) and Category naming

The COWAT assesses spontaneous word production under restricted search conditions (i.e. a category or a specific letter of the alphabet), and constitutes an assessment of verbal association fluency (Strauss et al., 2006). Phonemic fluency tasks, such as the COWAT, form part of the Multilingual Aphasia Examination (Benton, 1994), which includes a test of verbal fluency, an aspect of oral expression (Strauss et al., 2006). The F-A-S test, with commonly used letter fluency stimuli 'F', 'A', and 'S', is a measure of phonemic fluency; and the Animal Fluency task, with 'animals' commonly used as a category cue, is a measure of semantic fluency (Gladsjo et al., 1990; Strauss et al., 2006).

For the F-A-S task, participants are required to orally generate as many words as possible beginning with a specified letter (i.e. ‘F’, ‘A’, and ‘S’), excluding proper nouns, numbers and the same word with a different suffix, in a one minute period, for each specified letter (Lezak et al., 2004; Strauss et al., 2006). The score is derived by summing all acceptable words for the three letters (Lezak et al., 2004; Strauss et al., 2006). For the Animal Fluency task, participants are required to orally generate as many animal names as possible in a one- minute period. The score is calculated by summing all acceptable words (Strauss et al., 2006). Both tasks can be administered to individuals 7 years and older and each task takes about 5 minutes to complete (Strauss et al., 2006).

The F-A-S task has high internal consistency and adequate test-retest reliability (Harrison, Buxton, Husain, & Wise, 2000; Tombaugh, Kozak, & Rees, 1999) and scores on the F-A-S task have been found to correlate significantly with scores on similar phonemic fluency tasks (Harrison et al., 2000) as well as the above-named Animal Fluency task (Tombaugh, Kozak, & Rees, 1999).

Demographic variables, including age, education, reading level, gender, ethnicity and IQ reportedly have an influence on performance on the above-named fluency tasks (Harrison et al., 2000; Mitrushina et al., 1999; Strauss et al., 2006; Tombaugh et al., 1999).

The COWAT and category naming tasks have previously been administered in samples of youth, including trauma-exposed youth with and without PTSD (Ahmed et al., 2012; Schoeman et al., 2009), children and adolescents diagnosed with ADHD and severe mood dysregulation (Uran & Kiliç, 2015) and clinical youths (Hill et al., 2013).

(xi) The Tower of London (TOL)

Tower tests are commonly used to measure planning ability or the ability to plan ahead, and factors including working memory, response inhibition and visuo-spatial memory are necessary for successfully performing these tests (Phillips, Wynn, Gilhooly, Della Sala, & Logie, 1999; Strauss et al., 2006). The TOL is a performance-based task tapping aspects of executive function (Culbertson & Zillmer, 2001; MacAllister et al., 2011).

In terms of the TOL, two wooden boards are used, one containing three coloured (i.e. red, green, and blue) wooden balls that the examiner places in the goal position; and the second board, also containing three coloured wooden balls, is placed in front of the participant, who is required to rearrange the balls from a standard ‘start’ position to the examiner’s model (Strauss et al., 2006). The coloured balls must be moved, one at a time, from an initial start position to match a certain goal state (Phillips et al., 1999). Ten trials are presented and two minutes are allowed for each of the trials (Strauss et al., 2006). The accuracy of planning is assessed in terms of the number of moves that are made in excess of the minimum required to solve the problem (Phillips et al., 1999).

Moderate to high internal consistency for the total move score and adequate temporal reliability has been reported (Culbertson & Zillmer, 2001). Furthermore, validity of the TOL has been established (Culbertson & Zillmer, 1998, 2001; Larochette, Benn, & Harrison, 2009). A few demographic variables have been found to influence performance on the WMS-R, including age (Lee, Anderson, Dennerstein, Hendereson, & Szoek, 2013) and education (Rognoni et al., 2013).

The TOL has previously been administered in samples of youth, including, children and adolescents diagnosed with epilepsy (MacAllister et al., 2011), adolescents with traumatic brain injury and healthy controls (Donders & Larsen, 2012), children and adolescents with varying academic difficulties (Sikora, Haley, Edwards, & Butler, 2002), and university students undergoing psycho-educational assessments (Larochette et al., 2009).

3.2.6 Neuroimaging tasks

3.2.6.1 Self-report instruments

(i) The State-Trait Anxiety Inventory – State anxiety measure (STAI-S)

The STAI-S was used to provide a measure of the presence and severity of current anxiety symptoms experienced by participants prior to, on the same day, as the neuroimaging assessment. In addition, an adapted version of the STAI-S was administered to the participants directly after completion of the neuroimaging assessment. Original STAI-T items such as ‘at this moment I feel calm’ or ‘at this moment I feel frightened’ were adapted to ‘I felt calm in

the scanner’ and ‘I felt frightened in the scanner’. This was used to retrospectively assess the presence and severity of current anxiety symptoms experienced by the participant whilst he or she was in the scanner.

(ii) Measure of state anxiety in the scanner

Participants were asked to indicate their level of current anxiety midway through their neuroimaging assessment so as to provide an indication of their current level of state anxiety within the scanner. To obtain this measure of current state anxiety within the scanner, participants were asked the following: “On a scale of ‘0’ to ‘10’, with ‘0’ indicating ‘no anxiety’ and ‘10’ indicating ‘extreme anxiety’, how anxious are you currently feeling in scanner?”

3.2.6.2 International Affective Picture System (IAPS) task

The IAPS task allows for the assessment of brain activation during basic emotion processing (Van Buuren, Vink, Rapcencu, & Kahn, 2011). Brain activation, with particular focus on activation of the amygdala, hippocampus, and insula, was measured with fMRI whilst participants viewed and, immediately thereafter, rated images (i.e. positive, neutral or negative) from the IAPS (Lang, Bradley, & Cuthbert, 1997).

The experimental task consisted of the presentation of images from the IAPS which were categorized into three conditions, namely, positive, neutral and negative, according to validated ratings of the IAPS (Van Buuren et al., 2011). Each of the three conditions contained 32 images (Van Buuren et al., 2011). Participants were instructed to view each of the pictures for two seconds, and after viewing, were instructed to rate the image (maximum of two seconds) as positive, neutral or negative, by pressing one of three buttons on the response box provided to them when in the scanner (Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). A fixation cross appeared on the screen after each response and appeared for the remaining trial duration (Van Buuren et al., 2011; Vink, Derks, et al., 2014). The task contained four activation blocks which consisted of 96 seconds each, interleaved with four baseline rest blocks (i.e. a fixation cross on the screen for 32 seconds) (Vink, Derks, et al., 2014). Eight images of each condition were presented in pseudo-random order, resulting in a total of 24 pictures in each activation block (Vink, Derks, et al., 2014).

Participants were trained on the IAPS prior to the fMRI experiment. The duration of the task in the scanner was 9 minutes.

3.2.6.3 Stop-Signal Anticipation Task (SSAT)

For the purposes of the study's aims (i.e. with a focus on emotional responsiveness in adolescents with high and low levels of childhood maltreatment and AP), results of the SSAT are not included within this dissertation. Since the task was completed by the majority of participants in the study, a brief description of the task follows:

During the fMRI experiment, participants performed the SSAT (Zandbelt & Vink, 2010), a motor inhibition task (Vink et al., 2005) designed to invoke inhibitory control (Vink, Ramsey, Raemaekers, & Kahn, 2006) and to assess response inhibition (Zandbelt & Vink, 2010). The SSAT is based on the stop-signal paradigm (Logan & Cowan, 1984). In this paradigm, go-signals which necessitate a response are occasionally followed by a stop-signal, indicating that the planned response should be stopped (Zandbelt & Vink, 2010). The task therefore assesses the individual's ability to block or stop an intended movement at the last minute (Vink et al., 2006). Such inhibitory control is said to involve various mechanisms, namely, reactive mechanisms that are activated by the stop-signal, as well as proactive mechanisms which are active prior to a stop-signal being presented (Zandbelt, Van Buuren, Kahn, & Vink, 2011). Generally, participants tend to slow down their responding to go-stimuli when a stop-signal is anticipated, when there is a greater probability that they may need to stop (Vink, Zandbelt, et al., 2014; Zandbelt et al., 2011). Furthermore, deficits in proactive inhibition are reflected in a reduced effect of stop-signal probability on the go-signal response time, indicating a weaker anticipation of a stop-signal (Vink et al., 2006; Zandbelt et al., 2011). Participants were trained on the SSAT prior to the fMRI experiment.

3.2.7 Genotyping

3.2.7.1 Tier 1: Salivary DNA sampling

Saliva was collected from each of the participants in Tier 1 using the Oragene DNA OG-500 DNA collection kit (DNA, Genotek).

Participants were asked to refrain from eating, drinking or smoking for at least 30 minutes prior to the saliva being collected. Participants were then asked to stimulate salivary secretion by relaxing and rubbing their cheeks for 30 seconds. Participants were then required to deposit approximately 2 mL of saliva into the supplied collection tube, and to close the tube firmly. This action was required to break a seal within the vial, allowing the Oragene-DNA solution to mix with the saliva. Once the saliva is mixed with the Oragene-DNA solution, the saliva sample is stable at room temperature and can be stored at room temperature, in a long-term capacity (DNA, Genotek). DNA purification from 500 uL of the stabilized saliva sample could then proceed as per manufacturer's instructions.

3.2.7.2 Tier 2: Blood DNA sampling

At the first study visit, bloods were drawn from each participant by venous puncture and collected in two 10ml ethylene-diamine-tetra-acetic acid (EDTA) tubes. Samples were sent to the research laboratory within 24 hours of sampling where they were stored for further analysis.

3.2.8 Data Analysis

3.2.8.1 Statistical methods

Please refer to chapters 4, 5, and 6 for a description of the statistical methods and analyses employed to address each of the study's objectives.

3.2.8.2 Genetic data analysis: Tier 1

Purified DNA was quantified using spectrophotometric readings taken with the NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Inc.).

(i) 5-HTTLPR genotyping

Please see Appendix A1 ('Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents') for genotyping procedures.

(ii) BDNF *Val66Met* genotyping

Samples underwent automated genotyping. BDNF variants were genotyped using the Sequenom iPLEX Gold Genotyping Technology at The McGill University and Génome Québec Innovation Centre (Montreal, Canada) (McGill University and Génome Québec Innovation Centre, 2013).

3.2.8.3 Neuroimaging analysis (IAPS task)

Please refer to chapter 5 for analysis relating to image pre-processing, first-level analysis, and region of interest analysis.

3.2.9 Ethical considerations

Approval to conduct the study was obtained from the Health Research Ethics Committee at Stellenbosch University (See Appendix B1). In addition, permission to conduct the study and access the various secondary schools within the four educational districts of Cape Town was obtained from the Research Directorate of the Department of Education (See Appendix B2).

The study was conducted in accordance with The Declaration of Helsinki (World Medical Association, 2008) and Medical Research Ethical Guidelines on Human Research Version 2 (2002). Written informed consent and assent were obtained, respectively, from the parent/legal guardian of the participants and from the participants themselves, prior to inclusion in the study.

Participants were informed about the objectives and purposes of the study. Additionally, they were informed that their participation in the study was entirely voluntary and that they could withdraw from the study at any stage; that the information that they provided would be kept confidential; and that their anonymity would be maintained.

Although this was a low risk study, some of the study procedures could potentially cause discomfort. It was explained to participants both verbally and in the informed consent and assent documents that if they became emotionally distressed during the clinical interviews or requested counseling, an appropriate referral would be made. Furthermore, participants were

informed that they could decline to answer any questions and that if they felt fatigued they could freely request to have a break at any time during the assessments. Participants were also informed that the blood draw could potentially involve the risk of pain and bruising and that they could decline to provide a blood sample, as this was optional.

Despite there being no direct benefits for participants, they were informed of the potential future benefits for the prevention of anxiety disorders. Information gleaned from the study could potentially provide a better understanding of the development of anxiety disorders in youth and could result in the development of ways to potentially reduce the risk of developing an anxiety disorder(s) in youth, as well as inform new treatments for anxiety disorders.

In terms of the study documentation and data, the study database and related participant documentation were suitably coded so as to maintain participant confidentiality and anonymity. Access to participant information was permitted only to study staff. Additionally, participant files were kept in a secure office within a locked filing cabinet.

The following three chapters (i.e. chapters 4, 5, and 6) address the main study aims.

Chapter 4 is titled ‘The effects of childhood maltreatment and anxiety proneness on neuropsychological performance in non-clinical older adolescents’. This chapter addresses the first aim of the study (i.e. the predictive ability of CM and AP, as well as the combined effect of CM and AP, on neuropsychological performance, in healthy adolescents with high and low levels of CM and high and low levels of AP). This chapter has been submitted as a research paper to Child Abuse and Neglect and is currently under review.

Chapter 5 is titled ‘Emotion processing in a non-clinical sample of older adolescents with high and low levels of both anxiety proneness and childhood maltreatment: An exploratory neuroimaging study’. This chapter addresses the second aim of the study (i.e. a comparison of brain functional activity among healthy adolescents with high and low levels of CM and high and low levels of AP). This chapter has been prepared as a research paper and will be submitted to a relevant journal.

Chapter 6 is titled ‘Gene-by-environment interaction of BDNF *Val66Met* polymorphism and childhood maltreatment on anxiety proneness in a mixed race adolescent sample’. This chapter

addresses the final aim of the study in part (i.e. the interaction of the Brain Derived Neurotrophic Factor (BDNF) polymorphism in mediating AP). This chapter has been prepared as a research paper and will be submitted to a relevant journal.

Please refer to **Appendix A1** (Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents). This published manuscript addresses the interaction of the serotonin transporter gene and CM in mediating AS, which addresses the third aim of the study.

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CHAPTER 4

The effects of childhood maltreatment and anxiety proneness on neuropsychological performance in non-clinical older adolescents

(manuscript under review)

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Abstract

We explored the predictive ability of childhood maltreatment (CM) and anxiety proneness (AP), including the interaction of these variables, on a range of neuropsychological domains that have previously been reported on in maltreated youth and which, specifically, have been underexplored in anxiety-prone, non-clinical adolescents. 111 healthy adolescents participated, with 104 undergoing both neuropsychiatric and neuropsychological assessment. Multiple linear regression models were used to assess the unique and combined influences of CM and AP on neuropsychological performance. The interaction of CM and AP was associated with poorer performance in executive functioning skills (i.e. cognitive flexibility and verbal fluency), processing speed, and IQ. Both CM and AP were uniquely associated with verbal working memory performance, while verbal and visual memory performance and learning, as well as visuo-spatial ability, was not associated with either CM, AP, or the interaction of CM and AP. Our results suggest that increased levels of CM and AP may be risk factors for poor performance in a number of important neuropsychological domains. Our findings underscore the importance of assessing the impact of CM and anxiety-related temperamental traits on neuropsychological outcomes, given the unique and combined effects of CM and AP determined in our sample of healthy adolescents.

Keywords: neuropsychological performance, childhood maltreatment, anxiety proneness, adolescents.

Introduction

The periods of childhood, adolescence and early adulthood are associated with significant developmental changes (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009; Tamnes et al., 2010; Yurgelun-Todd, 2007) coupled with an increased risk for the development of anxiety, as evidenced by nationally representative household surveys and prospective community-based studies that have documented the onset of any anxiety disorder, or specific anxiety subtypes, across these critical developmental periods (Asselmann & Beesdo-Baum, 2015; Kessler et al., 2005; Merikangas, Nakamura, & Kessler, 2009; Pine, Cohen, Gurley, Brook, & Ma, 1998). The prevalence of DSM-IV anxiety disorders is high in adolescent and young adult samples, with cumulative lifetime rates ranging up to 30% (Asselmann & Beesdo-Baum, 2015). In addition, anxiety disorders are frequently comorbid (Merikangas et al., 2009), persistent, chronic conditions (Kessler et al., 2012), with childhood and adolescent anxiety disorders commonly associated with significant impairment, adverse functioning and disability in early adulthood (Asselmann & Beesdo-Baum, 2015; Essau, Lewinsohn, Olaya, & Seeley, 2014), including, increased interpersonal problems, poor health outcomes (Copeland, Angold, Shanahan, & Costello, 2014), and adverse psychosocial outcomes (Essau et al., 2014). Furthermore, anxiety in early adulthood is associated with adolescent anxiety as well as an increased risk of alcohol and substance use disorders (Essau et al., 2014).

A number of well-documented factors have been implicated in the aetiology of child and adolescent anxiety disorders (Murray, Creswell, & Cooper, 2009). These include biological vulnerability factors, such as the influences of gene variants (Domschke & Reif, 2012; Norrholm & Ressler, 2009); cognitive or information processing styles, such as attention, interpretation and memory biases (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007; Marques, Pereira, Barros, & Muris, 2013; Watts & Weems, 2006). Furthermore, environmental influences, reflective of negative and stressful life events and childhood maltreatment (CM)/trauma have been implicated (Benjet, Borges, & Medina-Mora, 2010; De Bellis & Thomas, 2003; Lewis, Byrd, & Ollendick, 2012; McCullough, Miller, & Johnson, 2010; Young & Dietrich, 2015); as have learning factors, such as social modelling (e.g. of parental anxious/avoidant behaviour) and information transfer (e.g. anxious parental communication with child) (Fisak & Grills-Tauechel, 2007). These vulnerability factors commonly influence or interconnect with one another (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010) to produce potentially maladaptive outcomes.

High anxiety proneness (AP) is characterized by high levels of self-reported anxiety-related temperamental traits in non-clinical individuals (Stein, Simmons, Feinstein, & Paulus, 2007) and include traits such as anxiety sensitivity (AS) (Reiss, Peterson, Gursky, & McNally, 1986) and trait anxiety (TA) (Eysenck, 1992). These are both developmentally stable risk factors for anxiety disorder (Garcia et al., 2013; Zavos, Gregory, & Eley, 2012; Zavos, Rijdsdijk, & Eley, 2012), with genetic influences exerting a greater effect on stability during adolescence and early adulthood than environmental influences, which are generally more age- or time-specific (Garcia et al., 2013; Zavos et al., 2012; Zavos et al., 2012). AS is defined as the individual's fear of anxiety-related or arousal-related sensations and symptoms (Reiss & McNally, 1985), stemming from the individual's belief that such sensations or symptoms may have negative consequences, such as feelings of embarrassment, illness or added anxiety (Reiss, Peterson, Gursky, & McNally, 1986), whereas TA refers to the individual's tendency to respond fearfully to stressors in general (McNally, 1989). AS is positively and significantly associated with both trait anxiety and neuroticism (Esteve & Camacho, 2008; Muris, Schmidt, Merckelbach, & Schouten, 2001) and both AS and TA are associated with anxiety disorders and associated symptoms in youth (McLaughlin, Stewart, & Taylor, 2007; Muris, Schmidt, Merckelbach, & Schouten, 2001; Schmidt, Zvolensky, & Maner, 2006; Weems et al., 2007). High AP in youth and young adults has been found to be associated with a number of negative outcomes, including, functional impairment in social and occupational domains (Korte, Brown, & Schmidt, 2013), and a range of negative health behaviours, including increased alcohol and drug use and dependence (Otto et al., 2016).

Information-processing theories of anxiety suggest that anxiety is associated with selective processing of information that is perceived as threatening or dangerous to the individual's personal wellbeing or safety (Beck & Clark, 1997). Both clinical anxiety and high AP are associated with increased levels of fear- or threat-related attentional bias, either towards or away from threat (Carmona et al., 2015; Dalglish et al., 2003; Puliafico & Kendall, 2006; Schoth, Golding, Johnson, & Lioffi, 2015), compared with non-anxious or low-anxious individuals (Bar-Haim et al., 2007; Eysenck, Derakshan, Santos, & Calvo, 2007; Telzer et al., 2008). Similarly, interpretation and memory biases are also evident in clinically anxious individuals and in children, adolescents and young adults with high AP (Muris & Field, 2008; Richards, Austin, & Alvarenga, 2001; Teachman, 2005; Watts & Weems, 2006). These information processing biases may be considered automatic as they are involuntary but they are not capacity-free and require cognitive resources (McNally, 1995). High-anxious individuals

therefore commonly employ more processing resources to task performance than low-anxious individuals and consequently have fewer available processing resources (Eysenck et al., 2007). Furthermore, a number of comparable outcomes on task performance have been reported in high-anxious and low-anxious individuals, however, anxiety is thought to reduce processing efficiency, with highly anxious individuals commonly reporting increased mental effort on task performance (Eysenck et al., 2007).

There have been few studies that have examined important aspects of neuropsychological functioning in adolescents with high levels of anxiety-related temperamental traits, and therefore, the literature reporting on the impact of AP on neuropsychological performance in healthy adolescents is relatively limited. Results from studies in adults indicate that traits such as neuroticism and TA are associated with deficits in working memory, verbal fluency, and IQ (Moutafi, Furnham, & Tsaousis, 2006; Qi et al., 2014; Sutin et al., 2011). Some evidence exists to indicate that certain neuropsychological domains are impacted by high levels of anxiety-related traits in youth. For example, in a sample of college students, Barnard et al. (2011) found that verbal working memory was significantly impacted by AS although mathematical and psychomotor performance were unaffected (Barnard, Broman-Fulks, Michael, Webb, & Zawilinski, 2011). Furthermore, visual working memory deficits have been found to correlate with symptoms of anxiety and depression in healthy children, and TA has been found to correlate with verbal working memory deficits in children and young adults (Aronen, Vuontela, Steenari, Salmi, & Carlson, 2005; MacLeod & Donnellan, 1993; Owens, Stevenson, Norgate, & Hadwin, 2008).

CM, which is associated with both AS and TA (Martin, Viljoen, Kidd, & Seedat, 2014), is a well-documented environmental risk factor for psychopathology across the life course (Collishaw et al., 2007; Kessler et al., 2010). The effects of anxiogenic events experienced during childhood are evident on various vulnerable brain regions (Hanson et al., 2013; Teicher et al., 2003) and are associated with dysfunctional neuropsychological processing that may persist into adulthood (Wilson, Hansen, & Li, 2011). Numerous studies have explored the effects of CM on neuropsychological performance in samples of youths grouped according to exposure status (i.e. CM exposed vs. non-exposed youths) [e.g. (Irigaray et al., 2013; Kirke-Smith, Henry, & Messer, 2014; Mothes et al., 2015)] and grouped according to exposure status and clinical disorder (i.e. CM exposed youth with clinical disorder(s), CM exposed youth without clinical disorder(s) and non-exposed, non-clinical youths) [e.g. (De Bellis, Hooper,

Spratt, & Woolley, 2009; De Bellis, Hooper, Woolley, & Shenk, 2010; De Bellis, Woolley, & Hooper, 2013; Kavanaugh & Holler, 2014b; Masson, East-Richard, & Cellard, 2015)], and others have compared neuropsychological functioning in youths with CM histories to youths with trauma histories other than CM (e.g. DePrince, Weinzierl, & Combs, 2009). Relatively few studies have assessed neuropsychological functioning in samples of healthy adolescents (Masson, Bussi res, East-Richard, R-Mercier, & Cellard, 2015) comprised of those with varying levels of CM. One such study demonstrated that non-clinical adolescents exposed to CM, quantified using Childhood Trauma Questionnaire scores, demonstrated deficits in aspects of executive functioning (Spann et al., 2012). Executive functioning can be defined as a set of control processes that regulate an individual's thoughts and actions (Miyake & Friedman, 2012) to achieve a certain goal in a flexible way (Funahashi, 2001). Executive functioning includes a number of cognitive processes, such as working memory, set shifting or task flexibility in information processing, and planning (Lezak, et al., 2012). Besides CM being associated with poorer executive functioning, the effect of CM on other neuropsychological domains in youth and adults is well established, with a history of CM being associated with poorer performance in attention, language, verbal episodic memory, working memory, visuo-spatial skills, and executive functioning (De Bellis et al., 2013; Irigaray et al., 2013; Kavanaugh & Holler, 2014b; Kirke-Smith et al., 2014; Nadeau & Nolin, 2013; Nolin & Ethier, 2007). Furthermore, both intellectual impairment and academic underachievement are frequently evident in maltreated children, adolescents, and young adults (De Bellis et al., 2013; Jones, Trudinger, & Crawford, 2004; Kavanaugh & Holler, 2014b; Maguire et al., 2015; Mills et al., 2011; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006; Perez & Widom, 1994). Comparable findings have been reported in severely maltreated adolescents who have demonstrated deficits in learning and memory, executive function, processing speed, working memory, visuo-perceptual function and language (Vasilevski & Tucker, 2016).

Given the evidence that exists for neuropsychological deficits in youths with maltreatment histories, as well as the limited studies of cognitive deficits in AP youths, the current study aimed to extend on these by exploring the predictive ability of AP and CM (including the interaction of these) on a number of important neuropsychological domains (i.e. IQ, visual and verbal memory and learning, executive functioning, processing speed, and visuo-spatial skills) in which deficits have previously been reported in maltreated youth, specifically, and which have been underexplored in AP, non-clinical adolescents.

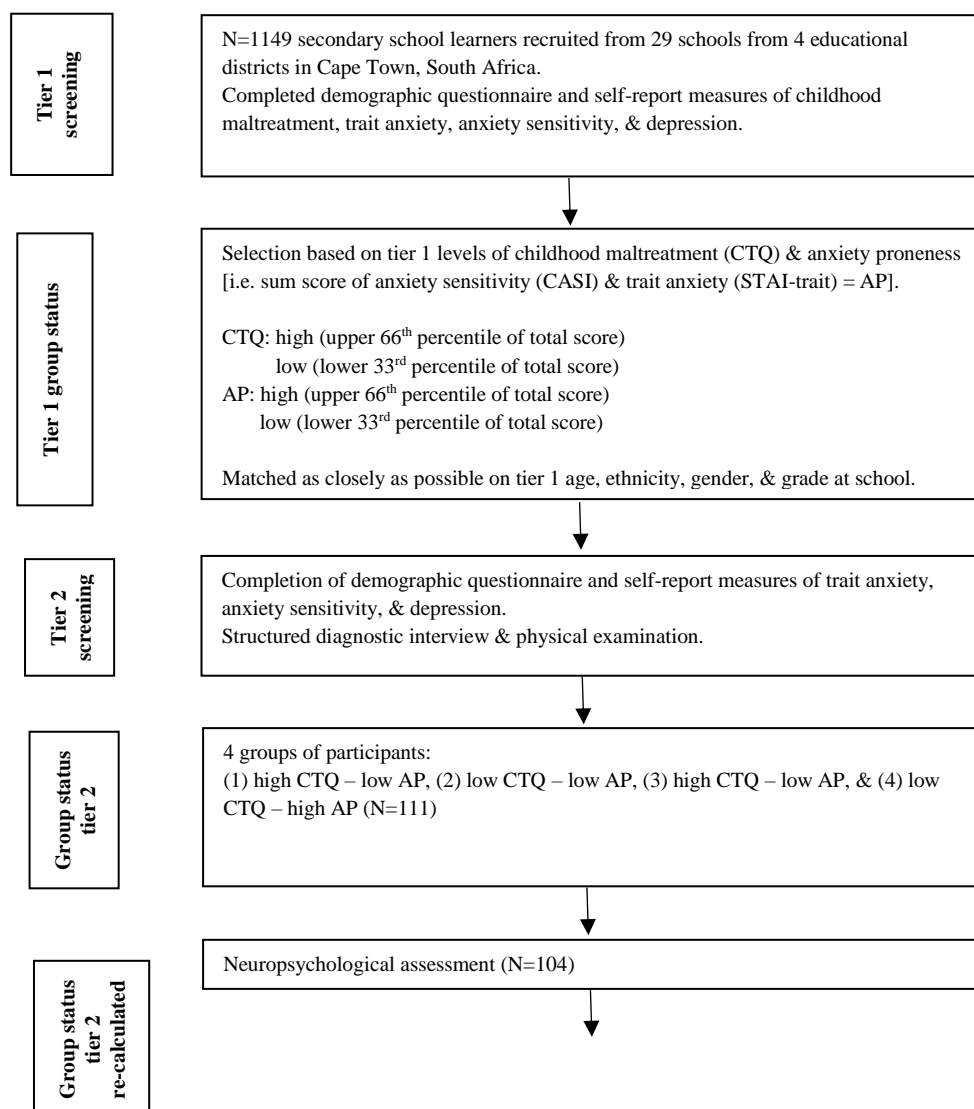
Methods and materials

Design

The present study was a two-tier study in a nonclinical sample of adolescents. In tier 1, stratified two-stage cluster sampling was employed, in which schools and learners within schools, from four educational districts in the Cape Town metropole, were randomly selected. A description of tier 1 methods are reported elsewhere (Martin et al., 2014).

Participants

Participants were included in the second tier of this study based on self-reported levels of both CM and AP established from data collected in the 1st tier. See Figure 1.



Participants grouped according to: tier 1 CTQ group status & tier 2 AP scores (i.e. high and low AP status based on the 50th percentile of tier 2 AP total score)

Figure 1. Flow diagram of sample selection and group categorization.

The tier 2 sample consisted of 111 healthy, non-clinical adolescents [mean age: 16.97($SD = 0.92$), range: 15-18 years], comprising predominantly females (82/111, 73.9%). Of the 111 participants, 98 were attending school at the time of their participation [mean grade: 10.74($SD = 1.02$), range: grades 9-12]. Those that were not attending school, had either completed grade 12 (12/111, 10.8%) or had dropped out of school (1/111, 0.9%). The majority of the sample self-identified as African (86/111, 77.5%), followed by mixed-race (24/111, 21.6%), and ‘other’ (1/111, 0.9%). Of the 111 participants included in the study, 104 underwent neuropsychological testing.

Eligible adolescents were (1) between 13 and 18 years of age, (2) able to read, write, and understand either English or Afrikaans at 5th grade level, (3) not currently taking any psychopharmacological medications, (4) willing and able to provide written informed assent, (5) medically well enough to undergo neuropsychological testing, (6) free of current or past bipolar disorder, schizophrenia or other psychotic disorders, or childhood disorders, (7) free of a current mood or anxiety disorder, (8) free of current alcohol or substance abuse or dependence, and (8) free of a history of head trauma.

Procedure

The study was approved by the Health Research Ethics Committee of Stellenbosch University, South Africa. All adolescents that participated in the second tier of the study were assessed at the Department of Psychiatry, Stellenbosch University and underwent a screening assessment (which included a structured diagnostic interview to assess for current and lifetime psychiatric disorders, the completion of a demographic questionnaire and various self-report measures, a physical examination, and a comprehensive neuropsychological assessment).

Measures

Screening assessment

Participants completed a demographic questionnaire which enquired, amongst others, about participants' age, gender, ethnicity, whether they were currently attending school, current grade at school, and socio-economic status (SES). To provide a measure of SES, participants were required to indicate whether or not they had access to basic household necessities in the home in which they resided (e.g. a tap with hot running water, stove, fridge, television, flush toilet, slept on their own bed, adequate amount of food, access to electricity/gas, and whether they were adequately clothed). Responses to these questions were dichotomous (i.e. 'yes' or 'no', coded '1' for 'yes' and '0' for 'no') with a greater score reflective of a higher socio-economic status. This scale has previously been used in a sample of South African youth (Gregorowski et al., 2016).

Current and lifetime psychiatric disorders were evaluated using the Mini-International Neuropsychiatric Interview-Kid for children and adolescents (MINI-KID, Sheehan et al., 2010). Self-report instruments comprised the following: (1) the Childhood Anxiety Sensitivity Index (CASI, Silverman, Fleisig, Rabian, & Peterson, 1991), an 18-item instrument that measures the fear of anxiety symptoms and is designed for use with school-age children and adolescents (Silverman et al., 1991); (2) the trait version of the State-Trait Anxiety Inventory (STAI, Spielberger et al., 1983), a 20-item instrument that assesses an individual's predisposition to be anxious (Julian, 2011; Spielberger et al., 1983); (3) the Childhood Trauma Questionnaire – Short Form (CTQ-SF, Bernstein et al., 2003), a brief, 28-item retrospective self-report measure of the frequency of abuse and neglect experienced prior to age 18 years. The CTQ-SF consists of 5 subscales, each consisting of five items, that assess emotional, physical, and sexual abuse and emotional and physical neglect, respectively (Bernstein et al., 2003); and (4) the Children's Depression Inventory (CDI, Kovacs, 1985), a brief 27-item self-report measure that assesses the amount and severity of depressive symptoms in children and adolescents (Kovacs, 1985). The screening assessment took approximately 1.5 hours to complete. Participants were given adequate rest breaks during the assessment to minimize fatigue.

Neuropsychological assessment

The neuropsychological test battery comprised tests of IQ, visual and verbal episodic memory and learning, executive functioning, processing speed, and visuo-spatial skills.

Full-scale IQ was determined using the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) two-subtest form consisting of the Vocabulary and Matrix Reasoning subtests. In terms of memory and learning, verbal memory and learning were assessed with the Rey Auditory Verbal Learning Test (RAVLT, Rey, 1941), and visual memory was assessed with the Rey-Osterreith Complex Figure Test (ROCF, Rey, 1941). Processing speed was assessed with the Trail Making Test part A (TMT-A, Reitan, 1958, 1979). In terms of executive functioning, the Trail Making Test part B (TMT-B, Reitan, 1958, 1979) was used to assess cognitive flexibility, the Controlled Oral Word Association Test (COWAT) (Spreen & Strauss, 1998) was used to assess verbal fluency, and the Digits Backward test of the Senior South African Individual Scale-Revised (SSAIS-R, Van Eeden, 1997) was used to assess verbal working memory. Visuo-spatial skills were assessed with the ROCF test (Rey, 1941) and the Block Design subtest of the SSAIS-R (Van Eeden, 1997). See Table 1 for neuropsychological domains assessed and neuropsychological tests used to assess domains. Hand dominance was determined with the Edinburgh Handedness Inventory (EHI, Oldfield, 1971) All participants were right-handed. The neuropsychological assessment took approximately 2 to 2.5 hours to complete. Participants were provided rest breaks as well as a lunch break of approximately 30 minutes, to minimize fatigue.

Table 1

Neuropsychological tests used to assess neuropsychological domains.

Neuropsychological domain	Neuropsychological test
IQ	WASI
Visual & verbal episodic memory & learning	
Verbal memory (immediate & delayed)	RAVLT
Visual memory (immediate & delayed)	ROCF
Learning	RAVLT words learnt
Processing speed	TMT-A
Executive functioning	
Cognitive flexibility	TMT-B
Verbal fluency	COWAT
Verbal working memory	Digit span (backward)
Visuo-spatial skills	
Complex visuo-spatial constructional ability	ROCF
Visuo-spatial skills and non-verbal concept formation	Block design

Data analyses

Data analyses were conducted using STATISTICA version 13 (StatSoftInc.) and the Statistical Package for Social Sciences (SPSS) version 23. Univariate normality was determined for all demographic and clinical variables. Descriptive statistics were computed for demographic and clinical variables, with variables of interest including age, gender, ethnicity, whether participants were attending school, current grade at school, SES; as well as AP (calculated by summing the total scores on the CASI and STAI-T), CM, and self-reported depression.

Analysis of variance (ANOVAs) was used to assess whether continuous variables of interest (e.g. clinical and neuropsychological scores) differed by gender and ethnicity. Pearson's correlation statistic was used to determine whether there were significant associations between continuous variables (e.g. between AP scores and self-reported depression scores). Multiple linear regression was used to assess whether AP and CTQ (as well as the interactive effect of AP and CTQ) were predictive of neuropsychological test scores. Ethnicity, SES, and depression scores were controlled for in the multiple regression analyses. Statistical significance was set at $p < 0.05$. If significant main effects or interaction effects were determined, mean plots of the groups (i.e. lower and higher AP, and lower and higher CTQ) were presented to visually display the significant linear regression findings.

Results

Characteristics of the sample

See Table 2 for sociodemographic and clinical characteristics of the sample. Mean scores for clinical variables were as follows: AP: 75.94 ($SD = 13.06$), CTQ: 44.97 ($SD = 18.23$), and CDI: 7.98 ($SD = 6.07$). In terms of the CTQ subscales, emotional neglect was most frequently endorsed by the sample ($M = 10.67$, $SD = 5.44$), followed by emotional abuse ($M = 9.68$, $SD = 5.08$), physical neglect ($M = 8.75$, $SD = 3.88$), physical abuse ($M = 8.66$, $SD = 5.19$) and sexual abuse ($M = 7.21$, $SD = 4.30$). See Table 3 for severity of abuse and neglect types reported by the sample. In terms of physical neglect and physical abuse, approximately one-fifth of the sample had scores in the severe/extreme range, with approximately 12 to 16% of the sample having scores in the severe/extreme range associated with sexual abuse, emotional neglect and emotional abuse. Information relating to both the onset and duration of maltreatment was not available.

Table 2

Sociodemographic and clinical characteristics of the total sample.

Characteristics		M(<i>SD</i>)	Range	<i>n</i>	%
Age (years)		16.97(0.92)	15-18		
Gender (female)				82	73.9
Ethnicity	African			86	77.5
	Mixed race			24	21.6
	Other			1	0.9
SES		11.74(2.39)	6-16		
Attending school (yes)				98	88.3
Grade at school		10.74(1.02)	9-12		
AP		75.94(13.06)	42-105		
	AS	35.96(6.70)	19-49		
	TA	39.97(8.24)	20-60		
CTQ total		44.97(18.23)	25-92		
	physical neglect	8.75(3.88)	5-23		
	emotional neglect	10.67(5.44)	5-23		
	emotional abuse	9.68(5.08)	5-23		
	physical abuse	8.66(5.19)	5-24		
	sexual abuse	7.21(4.30)	5-23		

CDI	7.98(6.07)	0-26
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Note: SES = socioeconomic status; AP = anxiety proneness; AS = anxiety sensitivity; TA = trait anxiety; CTQ = Childhood Trauma Questionnaire; CDI = Child Depression Inventory.

Table 3

Severity of abuse and neglect types reported by the sample (N=111).

Severity	EA	PA	SA	EN	PN
	(Frequency, % of sample)				
None or minimal	57 (51.4)	70 (63.1)	72 (64.9)	63 (56.8)	56 (50.5)
Low to moderate	28 (25.2)	9 (8.1)	13 (11.7)	19 (17.1)	18 (16.2)
Moderate to severe	8 (7.2)	10 (9.0)	13(11.7)	13 (11.7)	14 (12.6)
Severe to extreme	18 (16.2)	22 (19.8)	13 (11.7)	16 (14.4)	23 (20.7)

Note: EA = emotional abuse; PA = physical abuse, SA = sexual abuse, EN = emotional neglect, PN = physical neglect.

Bivariate correlations among variables

Table 4 displays correlations between the main study variables. A number of neuropsychological test scores were significantly intercorrelated ($p < 0.01$). For example, TMT-A scores were significantly correlated with ROCF immediate recall scores ($r = -0.30$, $p < 0.01$); and IQ scores were significantly correlated with RAVLT delayed recall scores ($r = 0.22$, $p < 0.05$), TMT-A scores ($r = -0.40$, $p < 0.01$), TMT-B scores ($r = -0.38$, $p < 0.01$), block design scores ($r = 0.56$, $p < 0.05$), digits backward ($r = 0.41$, $p < 0.01$) and COWAT scores ($r = 0.49$, $p < 0.01$). Despite these significant correlations determined among some of the neuropsychological tests, all tests associated with the various neuropsychological domains were included in the further analysis due to limited findings in non-clinical older adolescents with high AP and the limited findings in maltreated older adolescents with varying levels of CM. In terms of the significant intercorrelations determined, there was no evidence of multicollinearity as tolerance values were all above 0.2.

Table 4

Bivariate correlations between main study variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Age	-														
2 SES	0.04	-													
3 AP	-0.11	-0.28**	-												
4 CTQ	0.08	-0.15	0.24**	-											
5 CDI	-0.02	-0.13	0.66**	0.38**	-										
6 RAVLT IR	0.04	-0.03	-0.08	-0.13	-0.12	-									
7 RAVLT DR	-0.11	-0.04	0.05	-0.16	-0.01	0.39**	-								
8 RAVLT words learnt	-0.1	0.04	0.11	-0.06	0.08	-0.48**	0.37**	-							
9 ROCF IR	-0.06	0.06	-0.07	-0.08	0.04	0.02	0.22*	0.20*	-						
10 ROCF DR	-0.13	0.07	-0.07	-0.07	-0.01	-0.02	0.18	0.16	0.91**	-					
11 TMT-A	0.04	-0.07	0.02	0.11	-0.01	-0.09	-0.17	-0.12	-0.30**	-0.24*	-				
12 TMT-B	0.07	0.01	0.06	0.26**	0.1	-0.05	-0.17	-0.15	-0.18	-0.18	0.42**	-			
13 Block design	-0.12	0.18	-0.09	-0.18	0.04	0.04	0.14	0.20*	0.38**	0.40*	-0.33**	-0.32**	-		
14 Digits backward	0.04	0.15	-0.19	-0.23**	0.05	0.15	0.16	-0.01	0.14	0.13	-0.16	-0.40**	0.25*	-	
15 COWAT	0.13	0.15	-0.01	-0.09	0.1	0.05	0.05	0.14	-0.1	-0.13	-0.31**	-0.45**	0.28**	0.30**	-
16 IQ	-0.04	0.29**	-0.1	-0.25**	-0.09	0.19	0.22*	0.14	0.12	0.14	-0.40**	-0.38**	0.56*	0.41**	0.49**

Note: SES = socio-economic status; AP = anxiety proneness; CTQ = Childhood Trauma Questionnaire; CDI = Child Depression Inventory.

*Correlation is significant at the 0.05 level (2-tailed), **Correlation is significant at the 0.01 level (2-tailed).

Furthermore, significant correlations were evident between (1) self-reported depression and AP ($r = 0.66, p < 0.01$) and CM ($r = 0.38, p < 0.01$), and (2) SES and AP ($r = -0.28, p < 0.01$) and IQ ($r = 0.29, p < 0.01$); and therefore, both self-reported depression and SES were included in the multiple regression as covariates.

Analysis of variance outcomes

No gender differences were evident in terms of AP total score [$F(1, 109) = 0.926, p > 0.05$], CTQ total score [$F(1, 109) = 0.830, p > 0.05$], RAVLT immediate recall [$F(1, 102) = 0.127, p > 0.05$] and delayed recall [$F(1, 102) = 0.482, p > 0.05$], RAVLT words learnt [$F(1, 102) = 0.126, p > 0.05$], RCF immediate recall [$F(1, 102) = 2.091, p > 0.05$] and delayed recall [$F(1, 102) = 0.611, p > 0.05$], TMT-A [$F(1, 102) = 2.255, p > 0.05$] and TMT-B scores [$F(1, 101) = 0.999, p > 0.05$], block design [$F(1, 102) = 3.539, p > 0.05$], digit span backward [$F(1, 102) = 0.801, p > 0.05$], COWAT scores [$F(1, 102) = 0.106, p > 0.05$], and IQ scores [$F(1, 102) = 2.022, p > 0.05$].

In terms of ethnicity, significant differences in TMT-A scores [$F(1, 101) = 4.756, p < 0.05$], block design scores [$F(1, 101) = 6.477, p < 0.05$], digit span backward scores [$F(1, 101) = 5.239, p < 0.05$], and IQ scores [$F(1, 101) = 8.963, p < 0.05$] were evident. Ethnicity was therefore included as a covariate along with self-reported depression and SES in the multiple regression analyses.

CM, AP and their interaction as predictors of neuropsychological outcomes

A series of multiple regression analyses were used to determine whether CM, AP, and the interactive effect of CM and AP predicted neuropsychological test outcomes. Covariates included in all the multiple regression analyses comprised SES, ethnicity, and depression scores. For each multiple regression, CM, AP, and the interaction effect (CM x AP), were entered simultaneously in one step as predictor variables and one of the 11 neuropsychological tests was entered as the outcome variable. See Table 5 for results (adjusted β coefficients, standard errors, t -values, and p -values).

Table 5

Multiple regression results.

Domain assessed	Predictor variable	Outcome variable	β	SE	t	p -value
IQ	AP	WASI IQ	-0.61	0.31	-1.96	0.052
	CTQ		-1.31	0.55	-2.39	0.020
	AP x CTQ		1.69	0.71	2.39	0.019
Memory and learning						
Verbal memory	AP	RAVLT IR	0.05	0.11	-0.05	0.960
	CTQ		0.03	0.09	0.04	0.970
	AP x CTQ		-0.04	0.77	-0.05	0.960
	AP	RAVLT DR	-0.04	0.34	-0.11	0.910
	CTQ		-0.34	0.59	-0.57	0.570
	AP x CTQ		0.22	0.77	0.29	0.780
Learning	AP	RAVLT words learnt	-0.25	0.33	-0.75	0.452
	CTQ		-0.75	0.59	-1.26	0.210
	AP x CTQ		0.89	0.77	1.16	0.248
Visual memory	AP	ROCF IR	-0.25	0.34	-0.73	0.470
	CTQ		-0.25	0.59	-0.42	0.680

	AP x CTQ		0.29	0.77	0.38	0.710
	AP	ROCF DR	-0.31	0.34	-0.91	0.370
	CTQ		-0.16	0.59	-0.77	0.450
	AP x CTQ		0.6	0.77	0.78	0.440
Processing speed	AP	TMT-A	0.78	0.32	2.44	0.016
	CTQ		1.51	0.57	2.67	0.008
	AP x CTQ		-2.06	0.73	-2.81	0.006
Executive functioning						
Cognitive flexibility	AP	TMT-B	0.59	0.32	1.82	0.072
	CTQ		1.36	0.57	2.38	0.019
	AP x CTQ		-1.56	0.74	-2.11	0.037
Verbal fluency	AP	COWAT	-0.69	0.33	-2.13	0.036
	CTQ		-1.26	0.57	-2.19	0.030
	AP x CTQ		1.58	0.74	2.13	0.036
Verbal working memory	AP	Digits backward	-0.89	0.31	-2.84	0.006
	CTQ		-1.17	0.55	-2.12	0.036
	AP x CTQ		1.37	0.71	1.92	0.058
Visuo-spatial skills						
Visuo-spatial skills & non-verbal concept formation	AP	Block design	-0.34	0.33	-1.04	0.299
	CTQ		-0.45	0.58	-0.78	0.434

	AP x CTQ	0.6	0.75	0.8	0.423
Complex visuo-spatial constructional ability (see 'visual memory')	ROCF				

Note: AP = anxiety proneness total score; CTQ = Childhood Trauma Questionnaire total score.

Intelligence (IQ)

The interactive effect of AP and CTQ on IQ scores was significant (AP x CTQ: adjusted $\beta = 1.69$, SE = 0.71, $p < 0.05$). This finding indicates that when levels of AP are high, CM levels appear to have no effect on IQ, however, when AP levels are low, high levels of CM are associated with lower IQ scores than when CM levels are low. See Figure 2.

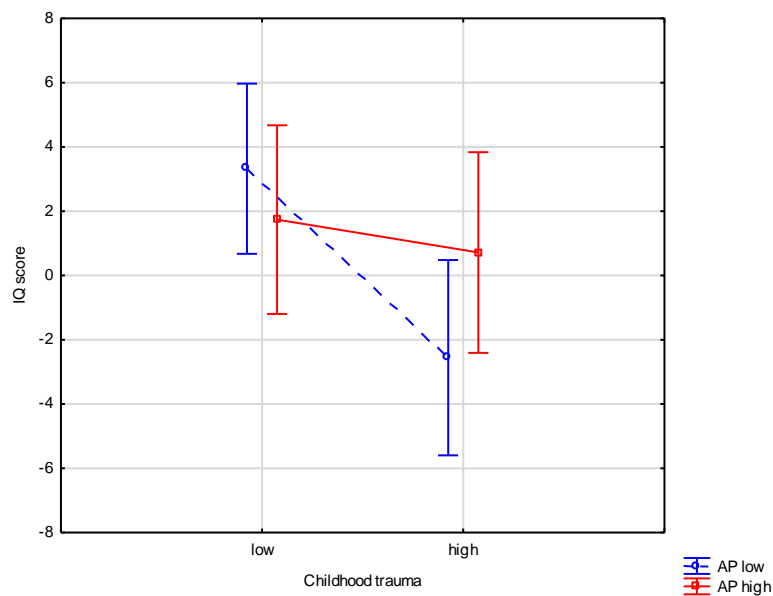


Figure 2. Interaction effect of AP and CTQ on IQ scores ($p < 0.05$).

Verbal memory

No main effects of AP or CTQ on RAVLT immediate and delayed recall scores were determined ($p > 0.05$). The interactive effect of AP and CTQ on RAVLT immediate and delayed verbal memory was non-significant ($p > 0.05$). These non-significant findings indicate that neither AP nor CTQ scores (including the interactive effect of these) are associated with verbal memory performance.

Visual memory

No main effects of AP or CTQ on ROCF immediate and delayed recall scores) were determined ($p > 0.05$). The interactive effect of AP and CTQ on ROCF immediate and delayed recall scores

was non-significant ($p>0.05$). These non-significant findings indicate that neither AP nor CTQ scores (including the interactive effect of these) are associated with visual memory performance.

Learning

No main effects of AP or CTQ on RAVLT words learnt scores were determined ($p>0.05$). The interactive effect of AP and CTQ on RAVLT words learnt scores was non-significant ($p>0.05$). These non-significant findings indicate that neither AP nor CTQ scores (including the interactive effect of these) are associated with the number of words learnt.

Processing speed

The interactive effect of AP and CTQ on TMT-A scores was significant (AP x CTQ: adjusted $\beta = -2.06$, $SE = 0.73$, $p<0.05$). This finding indicates that when levels of AP are high, CM levels appear to have no effect on processing speed performance, however, when AP levels are low, high levels of CM are associated with slower processing speed than when CM levels are low. See Figure 3.

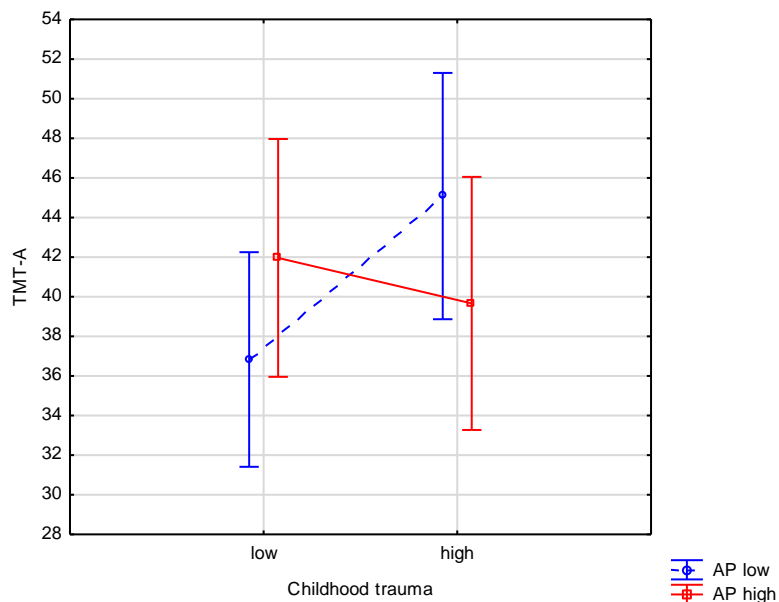


Figure 3. Interaction effect of AP and CTQ on TMT-A scores ($p<0.05$).

Cognitive flexibility

The interactive effect of AP and CTQ on TMT-B scores was significant (AP x CTQ: adjusted $\beta = -1.56$, SE = 0.74, $p < 0.05$). This finding indicates that when levels of AP are high, CM levels appear to have no effect on cognitive flexibility, however, when AP levels are low, high levels of CM are associated with lower cognitive flexibility scores than when CM levels are low. See Figure 4.

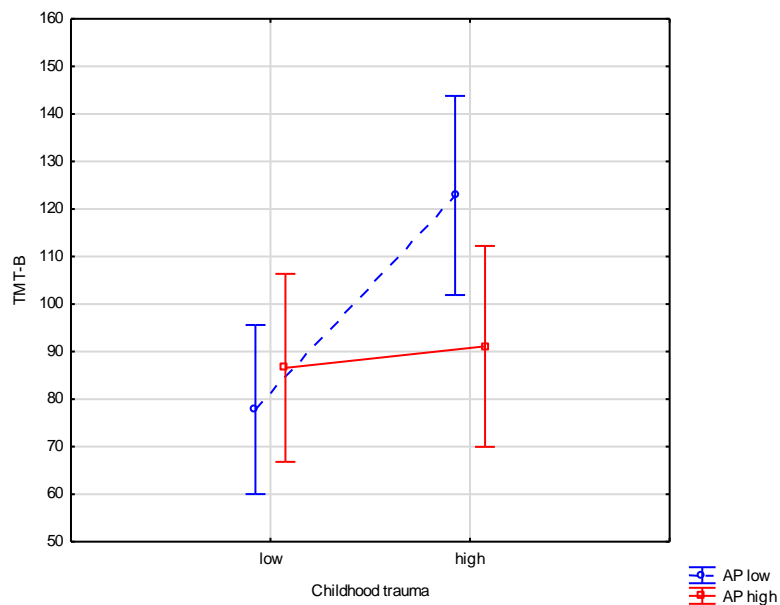


Figure 4. Interaction effect of AP and CTQ on TMT-B scores ($p < 0.05$).

Verbal fluency

The interactive effect of AP and CTQ on COWAT scores was significant (AP x CTQ: adjusted $\beta = 1.58$, SE = 0.74, $p < 0.05$). This finding indicates that when levels of AP are high, CM levels appear to have no effect on verbal fluency, however, when AP levels are low, high levels of CM are associated with lower verbal fluency scores than when CM levels are low. See Figure 5.

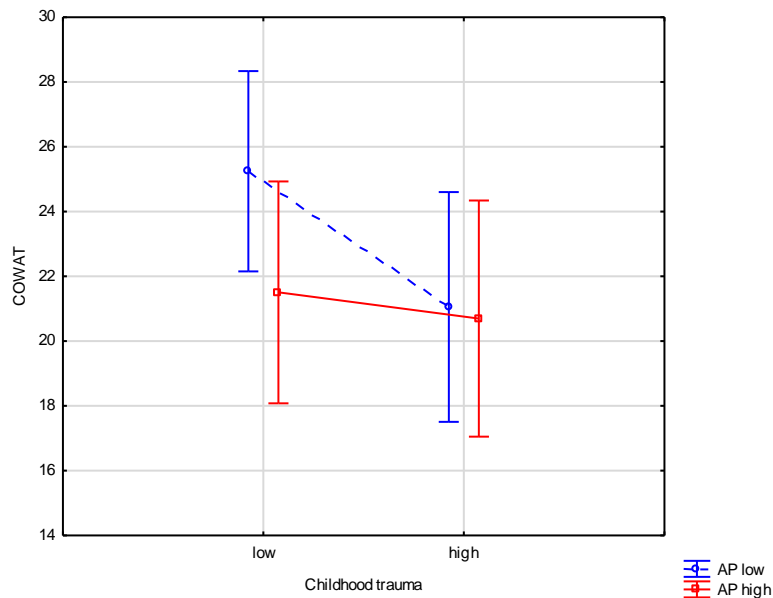


Figure 5. Interaction effect of AP and CTQ on COWAT scores ($p < 0.05$).

Verbal working memory

Main effects of AP and CTQ on digits backward scores were evident (AP: adjusted $\beta = -0.89$, $SE = 0.31$, $p < 0.05$; CTQ: adjusted $\beta = -1.17$, $SE = 0.55$, $p < 0.05$). The interactive effect of AP and CTQ on digits backward scores was non-significant ($p > 0.05$). The findings of significant main effects of AP and CTQ indicate that a greater level of AP, as well as CM, is associated with lower verbal working memory performance.

Visuo-spatial skills and non-verbal concept formation

No main effects of AP or CTQ on block design scores were determined ($p > 0.05$). The interactive effect of AP and CTQ on block design scores was non-significant ($p > 0.05$). These non-significant findings indicate that neither AP nor CTQ scores (including the interactive effect of these) are associated with non-verbal concept formation performance.

Discussion

The current study aimed to explore the predictive ability of AP, CM and the interactive effect of AP and CM on a number of important neuropsychological domains in a sample of healthy,

non-clinical adolescents recruited from secondary schools in Cape Town, South Africa. Numerous studies have assessed neuropsychological performance in youth with maltreatment histories, yet few have assessed the effects of varying levels of CM on neuropsychological performance, and studies that have assessed neuropsychological performance in AP youth are few. Furthermore, to our knowledge, no studies to date have assessed the interactive effect of AP and CM on neuropsychological performance in healthy adolescents.

We determined that poorer performance in terms of executive functioning skills [i.e. cognitive flexibility (TMT-B) and verbal fluency(COWAT)] and processing speed (TMT-A), as well as lower IQ scores (WASI IQ), was associated with the interaction between AP and CM, while taking into account the effects of SES, ethnicity and self-reported depression. More specifically, our results suggest that performance in the above-named domains is affected by the level of CM in adolescents reporting lower levels of AP, with those adolescents reporting both lower levels of AP and higher levels of CM demonstrating lower scores on the above-named domains, compared with adolescents reporting both lower levels of AP and lower levels of CM. The finding that higher levels of CM in the presence of lower levels of AP (which may be considered relatively normative levels of AP) impact above named neuropsychological domains is in line with previous studies that have demonstrated the negative impact of CM on executive functioning abilities, processing speed, and IQ (De Bellis et al., 2009, 2013, Kavanaugh & Holler, 2014a, 2014b; Masson, Bussi eres, et al., 2015; Mothes et al., 2015). In support of our findings, a recent meta-analysis which examined the effect of maltreatment on neuropsychological performance in children, adolescents and adults, determined that CM effects were most pronounced in terms of executive functioning skills, speed of information processing, and intelligence (Masson, Bussi eres, et al., 2015).

Furthermore, our finding that neither higher nor lower levels of CM appeared to significantly impact cognitive flexibility, verbal fluency, processing speed, and IQ scores, when AP is high, highlights the detrimental effects of high levels of AP on neuropsychological performance, regardless of levels of CM. Indeed, it has been suggested that certain clinical variables, including levels of stress and subjective complaints, are important variables to consider in the assessment of the impact of CM on neuropsychological performance (Masson, Bussi eres, et al., 2015). Anxiety-related temperamental traits may be reflective of sub-threshold clinical presentations (Altınba  et al., 2015), and typically, individuals with high AP employ greater cognitive resources during performance tasks, frequently resulting in poorer processing

efficiency due to the reduced availability of processing resources (Basten, Stelzel, & Fiebach, 2012; Eysenck et al., 2007; Murray & Janelle, 2003). Such findings are consistent with neuroimaging studies that have reported neural activation differences in AP individuals during working memory task performance, in which AP individuals demonstrate lesser activation of the prefrontal regions than low AP individuals, particularly when memory load is high (Derakshan & Eysenck, 1998; Gawda & Szepietowska, 2016; Qi et al., 2014; Rypma, Berger, & D'Esposito, 2002). Furthermore, some neuroimaging studies have found no differences in behavioural data between low- and high-anxious individuals, yet differences at the neural level are evident (Basten et al., 2012; Gawda & Szepietowska, 2016), reflective of deficits in processing efficiency relative to performance effectiveness, in high anxious individuals (Nazanin Derakshan & Eysenck, 2009; Eysenck & Derakshan, 2011). In line with our findings, previous studies in individuals with increased levels of anxiety-related temperamental traits, such as TA and neuroticism, have reported deficits in working memory performance, processing speed, verbal fluency, and intelligence (Emerson et al., 2005; Moutafi et al., 2006; Qi et al., 2014; Rajchert et al., 2014; Sutin et al., 2011).

In addition to the findings above, we determined that verbal working memory performance was not impacted by the interaction of AP and CM, but rather that AP and CM were uniquely associated with performance. Higher levels of AP, as well as higher levels of CM, individually, were associated with poorer working memory performance, which is consistent with studies in both CM (Kavanaugh & Holler, 2014a) and AP (Barnard et al., 2011; Derakshan & Eysenck, 1998; Eysenck, Payne, & Derakshan, 2005). Lastly, our results suggest that neither CM nor AP (nor CM x AP) were predictive of verbal and visual memory performance and learning, or visuo-spatial performance, in our sample. These findings are consistent with studies in maltreated and non-maltreated older children and adolescents in which no differences in non-verbal and verbal memory and learning were noted (Irigaray et al., 2013), but are in contrast to previous studies that have noted deficits in these domains, particularly in samples of individuals with CM histories (Rivera-Vélez, González-Viruet, Martínez-Taboas, & Pérez-Mojica, 2014; Savitz, van der Merwe, Stein, Solms, & Ramesar, 2007; Vasilevski & Tucker, 2016). Inconsistent findings may be due to methodological differences across studies, including the assessment measures and populations investigated, such as the diversity of tasks used to assess specific neuropsychological domains, and the inclusion of youths with psychiatric disorders, respectively. Moreover, the neuropsychological assessment measures used to assess verbal and

visual memory and learning, and visuo-spatial skills, in this study, may have lacked sensitivity to detect differences in performance as an effect of AP and CM.

While the present study provides support for the individual and combined effects of CM and AP on a number of neuropsychological domains in non-Caucasian, healthy adolescents, results must be considered preliminary given the exploratory nature of the study. A number of study limitations should be noted. First, our study relied on self-report measures to determine participants' levels of CM, AP, and depression, which may have resulted in over- or under-reporting of symptoms. Second, as the CTQ-SF is a retrospective self-report measure of CM, moderate recall bias may have been introduced. Thirdly, the neuropsychological evaluation was conducted in English or Afrikaans and not in the Xhosa language, the first language of the majority of African participants. Lower performance in certain neuropsychological tests may therefore have been overestimated, given that the assessment of neuropsychological performance is dependent on both language ability and language recognition (Olmedo, Berg, Mejnartowicz, & Walke, 2012). Fourthly, the majority of instruments utilized in this study have not been validated in a South African adolescent sample. Fifthly, the impact of important moderator variables, such as age of onset of maltreatment and duration of maltreatment, was not assessed. Finally, given that multiple corrections across analyses of neurocognitive domains was not employed, further research is necessary to confirm our significant findings. Despite these limitations, this study has a number of strengths. A structured diagnostic interview was conducted with all participants to assess for current and lifetime psychiatric disorders. In addition, we controlled for important clinical and demographic factors known to potentially influence neuropsychological performance, namely, depression, SES, and ethnicity. Furthermore, the assessment of both the individual and combined effects of CM and AP on neuropsychological performance extends previous findings and highlights the effects of CM under low and high AP conditions. Recommendations for future research include replication of the study in samples in which ethnic groups are better represented. In addition, assessment of both the individual and combined effects of AP and unique CM types, as well as concurrent forms of maltreatment, on neuropsychological outcomes, should be assessed in adolescent samples.

Conclusion

In summary, our results suggest that in healthy adolescents, increased CM and AP may be risk factors for poor performance in a number of important neuropsychological domains. The influence of CM on executive functioning skills (e.g. cognitive flexibility and verbal fluency skills), processing speed, and intelligence, is dependent on the level of AP. Adolescents reporting lower levels of AP are more vulnerable to the effects of CM, yet levels of CM do not appear to impact these domains when AP levels are high. Furthermore, CM and AP uniquely impact verbal working memory performance, however, CM, AP, and their interaction appear to not affect verbal and visual memory and learning, and visuo-spatial performance. Our findings underscore the importance of assessing the impact of levels of CM and anxiety-related temperamental traits on neuropsychological outcomes, given the unique and combined effects of CM and AP determined in our sample of healthy adolescents. Furthermore, our findings may have important clinical implications as neuropsychological deficits, such as impairments in executive functioning and episodic memory, are a core feature of psychiatric disorders, including anxiety disorders (Airaksinen, Larsson, & Forsell, 2005; Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & Lönnqvist, 2008). In addition, adolescents who demonstrate lower neuropsychological performance are at increased risk of poor academic performance, given established associations between, executive functioning and IQ, and school performance, including math and reading achievement (Best, Miller, & Naglieri, 2011; Diamantopoulou, Rydell, Thorell, & Bohlin, 2007; Mayes, Calhoun, Bixler, & Zimmerman, 2009).

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CHAPTER 5

Emotion processing in a non-clinical sample of older adolescents with high and low levels of both anxiety proneness and childhood maltreatment: An exploratory neuroimaging study (*manuscript in preparation*)

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Abstract

Background: fMRI studies suggest that both youth with maltreatment histories and youth with elevated levels of anxiety proneness demonstrate deficits in emotion processing. This is evidenced by increased functional responses to emotional stimuli in the amygdala and associated brain regions. No studies to date have examined emotion processing in healthy adolescents with high and low levels of both childhood maltreatment and anxiety proneness using positive, negative and neutral images from the International Affective Picture System. We investigated the potential unique and combined effects of childhood maltreatment and anxiety proneness on emotion processing in a non-clinical sample of adolescents.

Methods: Seventy-eight right-handed adolescents aged 15 to 18 years completed an fMRI emotion processing task in which they rated neutral, negative and positive images. Adolescents were categorized into four groups based on high and low levels of both childhood maltreatment and anxiety proneness. Task performance (i.e. image matching accuracy and reaction times) and functional activation in bilateral amygdala, hippocampus and insula, in response to viewing correctly matched emotionally salient images (i.e. positive and negative relative to neutral images), were assessed and compared across groups.

Results: Neither childhood maltreatment nor anxiety proneness scores were significantly correlated with either task performance or functional activation outcomes. No significant main effects (i.e. childhood maltreatment and anxiety proneness) or interaction effects (i.e. childhood maltreatment x anxiety proneness) were evident in terms of activation in the amygdala, hippocampus or insula in response to negative and positive images. Similarly, no significant main effects or interaction effects on task performance were evident and no significant differences in task performance (i.e. matching accuracy and reaction times) were observed across the four groups. A trend for greater activation in response to negative ($p=0.07$) and positive ($p=0.09$) images in the right amygdala was evident for those with high anxiety proneness levels compared with those with low anxiety proneness levels.

Conclusion: Healthy adolescents with high and low levels of childhood maltreatment and anxiety proneness perform comparably in terms of processing emotional content, such as negative and positive images, relative to neutral images. The trend for greater activation in response to emotionally salient (i.e. negative and positive) images in the right amygdala,

evident in those adolescents with heightened levels of anxiety proneness, irrespective of level of childhood maltreatment, suggests that right amygdala hyperactivity may be a neural correlate of anxiety proneness in healthy adolescents. Findings further suggest that childhood maltreatment did not have differential effects on emotion processing outcomes in this sample.

Keywords: fMRI, emotion processing, childhood maltreatment, anxiety proneness, adolescents, amygdala, hippocampus, insula.

Background

Adolescence may be considered a developmental period characterized by maturational improvements in a number of domains, such as social and cognitive functioning and physical competencies (Crone et al., 2006; Dahl, 2004; Steinberg & Morris, 2001) as well as considerable neural development, reflected in structural and functional changes and associated cognitive abilities (Blakemore, 2008; Blakemore & Choudhury, 2006; Giedd, 2004; Sturman & Moghaddam, 2011; Tamnes et al., 2010; Yurgelun-Todd, 2007). Adolescence may also be considered a period of relative instability in which difficulties associated with the control of both behaviour and emotional reactivity are evident (Casey et al., 2010; Dahl, 2004; Patterson, Dishion, & Yoerger, 2000). Furthermore, adolescence marks the period in which anxiety disorders, such as panic disorder, generalized anxiety disorder, social phobia, and agoraphobia, commonly have their onset (Asselmann & Beesdo-Baum, 2015; Merikangas, Nakamura, & Kessler, 2009), with temperamental disposition and environmental trauma and stress (Weems & Stickle, 2005) potentially making a significant contribution to these disorders (Mundy et al., 2015).

Anxiety proneness (AP), characterized by elevated levels of self-reported anxiety-related temperamental traits (Simmons, Strigo, Matthews, Paulus, & Stein, 2006), such as trait anxiety and anxiety sensitivity, is associated with a wide range of negative mental health outcomes, including anxiety symptoms and anxiety disorders in children, adolescents and adults (Mundy et al., 2015; Muris, 2002; Noël & Francis, 2011; Olatunji & Wolitzky-Taylor, 2009; Waszczuk, Zavos, & Eley, 2013). In addition, AP is associated with difficulties in emotion regulation (Kashdan, Zvolensky, & McLeish, 2008; Matt, Fresco, & Coifman, 2016), known to increase risk for psychopathology, including anxiety symptoms and disorders (Aldao, Nolen-Hoeksema, & Schweizer, 2010; Cisler, Olatunji, Feldner, & Forsyth, 2010). Both clinical and sub-clinical anxiety are associated with threat-related attentional bias (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van Ijzendoorn, 2007) and individuals with dispositional anxiety, for example, demonstrate a tendency to allocate attention towards threatening, potential threatening or negative stimuli (Bar-Haim et al., 2007; Koster, Crombez, Verschuere, Van Damme, & Wiersema, 2006; Nay, Thorpe, Roberson-Nay, Hecker, & Sigmon, 2004; Richards, French, Nash, Hadwin, & Donnelly, 2007; Telzer et al., 2008; Williams, Watts, MacLeod, & Mathews, 1997). Increased AP during adolescence and early adulthood, as reflected in increased trait anxiety and anxiety sensitivity, has been shown to be positively

associated with stressful life events (Aktekin et al., 2001; McLaughlin & Hatzenbuehler, 2009; Zavos et al., 2012).

Early childhood adversity is a well-documented environmental risk factor for the development of anxiety symptoms and anxiety disorders in youth and adults (Carr, Martins, Stingel, Lemgruber, & Juruena, 2013; Hovens et al., 2010; Lindert et al., 2014; McCullough, Miller, & Johnson, 2010). As with AP, CM is associated with both behavioural and emotional problems, as well as with deficits in emotional response and emotion regulation strategies (Arslan, 2016; D'Andrea, Ford, Stolbach, Spinazzola, & van der Kolk, 2012; Heleniak, Jenness, Vander Stoep, McCauley, & McLaughlin, 2016; Kaiser & Malik, 2015; Maughan & Cicchetti, 2002). Childhood trauma is also associated with attentional threat bias, either toward or away from threat (Kelly et al., 2015; Shackman, Shackman, & Pollak, 2007). The degree of attention to threat has been found to mediate the relationship between physical maltreatment and self-reported anxiety in youth (Shackman et al., 2007).

It is well documented that early life stress and adverse childhood experiences have profound and potentially enduring neural consequences on the brain, with the effects particularly evident on the hypothalamic-pituitary-adrenal (HPA) axis, and structural and functional disturbances evident in emotion and stress-regulating structures, including the amygdala and hippocampus (Anda et al., 2006; Rinne-Albers, van der Wee, Lamers-Winkelmann, & Vermeiren, 2013; Teicher et al., 2003; Whittle et al., 2013). The aforementioned neurobiological disturbances likely underpin the increased risk of psychopathology in individuals exposed to early life stress and adversity (Heim & Nemeroff, 2001; Heringa et al., 2013). Indeed, in terms of emotion processing, there is specificity of distinct neural structural and functional abnormalities and symptoms of psychiatric disorders (Phillips, Drevets, Rauch, & Lane, 2003), including anxiety disorders (Fonzo et al., 2015).

Functional magnetic resonance imaging (fMRI) studies and investigations of attentional capacities in youth have shown that youth and adults with documented CM histories have deficits in emotion processing compared with non-maltreated controls. These deficits, which are independent of trauma- and non-trauma-related psychopathology, are reflected in, for example, enhanced amygdala reactivity to facial expressions of emotion (e.g. angry and fearful faces) and salient images, enhanced response times to identifying negative stimuli, and less accuracy in recognizing both positive and neutral stimuli (Maheu et al., 2010; Masten et al.,

2008; Pollak, 2008; Pollak & Tolley-Schell, 2003; van Harmelen et al., 2013; Young & Widom, 2014). Neuroimaging studies of emotion processing in the context of CM have largely focused on limbic system reactivity in response to negative facial expressions of emotion. Studies in adult samples have demonstrated that the experience of CM is associated with an increased neural response to threat, reflected in increased amygdala connectivity with hippocampus and prefrontal cortex (Gold, Morey, & McCarthy, 2015; Jedd et al., 2015). In addition, studies in healthy non-clinical adults have established an association between CM and altered activity in the amygdala and insula, in response to negative emotional stimuli such as sad, angry and fearful faces (i.e. relative to neutral faces) (Dannlowski et al., 2012; Dannlowski et al., 2013; Redlich et al., 2015). Similarly, in youth, there is evidence to suggest that early life adversity is associated with altered functioning of medial temporal lobe regions. The amygdala responds to both negative and positive stimuli (i.e. happy, sad and fearful facial expressions), as determined in healthy youths and adults (Fusar-Poli et al., 2009) as well as in children with elevated levels of life stress (i.e. stressful and traumatic life events) (Suzuki et al., 2014). Children and adolescents who have experienced caregiver deprivation, emotional neglect, adverse rearing conditions, and early deprivation, demonstrate increased activation in the amygdala and hippocampus in response to the processing of fearful and angry faces (Maheu et al., 2010; Tottenham et al., 2011). Similarly, non-clinical children exposed to family violence demonstrate hyperactivation in the amygdala, as well as the insula, in response to threatening stimuli, such as angry faces, relative to neutral faces (McCrory et al., 2011).

Tasks employing facial expressions of emotion and tasks employing images from the International Affective Picture System (IAPS, Lang, Bradley, & Cuthbert, 1997) both activate similar brain structures (e.g. amygdala, hippocampus, prefrontal and visual cortex), however, tasks employing facial expressions of emotion are associated with a significantly greater amygdala response (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002) but less subjective arousal than IAPS images (Britton, Taylor, Sudheimer, & Liberzon, 2006). Moreover, it has been suggested that tasks employing facial expressions of emotion involve emotion recognition. In contrast, tasks that entail observing IAPS images are thought to involve the direct experience of emotion (Britton et al., 2006). In comparison with studies that have employed facial expressions of emotion to assess emotion processing in youth, relatively few studies have used images from the IAPS (Lang et al., 1997). Nevertheless, employing the IAPS, McLaughlin and colleagues (2015) noted that CM in adolescents, controlling for psychopathology, was associated with increased activation in the amygdala and insula,

amongst other regions, in response to negative, but not positive emotional stimuli (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). It has been suggested that hyper-reactivity in response to salient stimuli in aforementioned limbic structures represents both an adaptive response to persistent and unpredictable environmental danger or threat, as well as a risk factor associated with increased susceptibility to psychopathology, such as mood and anxiety disorders (Fonzo et al., 2016; McCrory et al., 2011; van Wingen, Geuze, Vermetten, & Fernández, 2011).

In terms of emotion processing in individuals with anxiety disorders (i.e. posttraumatic stress disorder, social anxiety disorder and specific phobia), despite variable findings, there remains strong evidence for altered amygdala and insula functioning in response to processing negative stimuli in adults (Etkin & Wager, 2007). In youth, an anxiety disorder diagnosis, such as generalized anxiety disorder and panic disorder, has been associated with amygdala hyperactivation to masked angry faces and non-masked angry and fearful faces (McClure et al., 2007; Monk et al., 2008; Thomas et al., 2001). Higher levels of trait anxiety have been found to be associated with increased amygdala reactivity in response to unattended fearful faces and masked fear in healthy young adults (Dickie & Armony, 2008; Etkin et al., 2004), yet no significant association between trait anxiety levels and activation in either the amygdala or hippocampus in response to non-masked fear was noted by Etkin and colleagues (2004). AP individuals demonstrate increased engagement of both lateral and medial prefrontal cortex to effectively decrease negative emotions (Campbell-Sills et al., 2011). Furthermore, AP individuals demonstrate increased amygdala and insula reactivity in response to emotional faces (Stein, Simmons, Feinstein, & Paulus, 2007). Atypical emotion regulation and emotion processing have also been noted in sub-clinical populations of older adolescents and young adults. In contrast to functional imaging studies that have reported on neural response differences in youth with maltreatment histories, findings of the impact of AP on brain function in emotion processing in pre-clinical adolescent populations, such as those with elevated levels of AP, is limited.

Of importance, amygdala, hippocampus, and insula hyperactivity as a function of exposure to salient stimuli (i.e. unpleasant facial expressions of emotion and unpleasant images) is not unique to individuals with histories of CM, clinical disorder, or sub-threshold anxiety, but is also evident in healthy, non-clinical youth and adults (Killgore & Yurgelun-Todd, 2005; Vink, Derks, Hoogendam, Hillegers, & Kahn, 2014). However, given the evidence that exists for

neural differences in emotion processing in both anxious youth and youth with maltreatment histories, determined predominantly in studies using tasks depicting facial expressions of emotion, we aimed to explore responses in the amygdala, hippocampus and insula during the processing of emotionally salient IAPS images, relative to neutral images, in healthy adolescents with high and low levels of CM and AP.

Methods

Design

This was a two-tier study in a nonclinical sample of adolescents. In tier 1, schools and attending students, from four educational districts in the Cape Town metropole, were randomly selected using stratified two-stage cluster sampling. A description of tier 1 methods has been reported elsewhere (Martin, Viljoen, Kidd, & Seedat, 2014).

Participants

Four groups of adolescents were selected for participation in the 2nd tier of the study based on self-reported levels of CM (as measured by the Childhood Trauma Questionnaire, CTQ-SF) and AP [measured by combining total scores on the Childhood Anxiety Sensitivity Index (CASI) and the trait version of the State-Trait Anxiety Inventory (STAI-T)], as determined from data collected in the 1st tier. Group status was initially determined by selecting participants who fell within the upper 66th and lower 33rd percentile for both CM and AP, respectively. These cut-offs were used to provide a clear delineation between high and low scorers. Participants were matched as closely as possible on the tier 1 sample with respect to age, ethnicity, gender, and educational status. Once all tier 2 data had been collected, group status was re-calculated by grouping participants according to their tier 1 CM status (i.e. either high or low) and using the 50th percentile of their tier 2 AP total score to determine high and low AP status. The 50th percentile was employed to categorize low and high AP adolescents to achieve more evenly distributed groups. Use of the 50th percentile to divide participants into those with relatively high and low levels of AP (i.e. high and low levels of anxiety sensitivity and trait anxiety) has been employed in several other studies (e.g. Basten, Stelzel, & Fiebach, 2012; Etkin et al., 2004; Fluharty, Attwood, & Munafo, 2015; Savostyanov et al., 2009; Schmidt & Lerew, 1998).

Eligible adolescents were (1) between 13 and 18 years of age, (2) able to read, write, and understand either English or Afrikaans at 5th grade level, (3) not currently taking any psychotropic medications, (4) willing and able to provide written informed assent, (5) medically well enough to undergo a neuroimaging assessment, (6) free of current or past bipolar disorder, schizophrenia or other psychotic disorders, or childhood disorders, (7) free of a current mood or anxiety disorder, (8) free of current alcohol or substance abuse or dependence, and (8) free of a history of head trauma.

Procedure

This study was approved by the Health Research Ethics Committee of Stellenbosch University, South Africa (ethics reference number: N10/11/370). Participants included in the 2nd tier of the study underwent a screening assessment (which included a structured diagnostic interview to assess for current and lifetime psychiatric disorders, the completion of a demographic questionnaire and various self-report measures, a physical examination and a blood draw), and neuropsychological and neuroimaging assessments at the Department of Psychiatry, Stellenbosch University. Prior to inclusion, written informed consent was obtained from participants' parents or legal guardians if they were younger than 18 years of age. In addition, informed assent was obtained from all participants.

Measures

Participants completed a demographic questionnaire which included, amongst others, age, gender, ethnicity, school attendance status, and current grade at school.

Current and lifetime psychiatric disorders were evaluated using the Mini-International Neuropsychiatric Interview-Kid for children and adolescents (MINI-KID, (Sheehan et al., 2010). Self-report instruments comprised the following: (1) the Childhood Anxiety Sensitivity Index (CASI, Silverman, Fleisig, Rabian, & Peterson, 1991), an 18-item instrument that measures the fear of anxiety symptoms in school-age children and adolescents (Silverman et al., 1991); (2) the State-Trait Anxiety Inventory (STAI, Spielberger et al., 1983), a 40-item instrument consisting of 2 subscales containing 20 items each, that assesses, respectively, current anxiety symptoms (i.e. state anxiety) and anxious disposition (i.e. trait anxiety) (Julian, 2011; Spielberger et al., 1983); (3) the Childhood Trauma Questionnaire – Short Form (CTQ-

SF, Bernstein et al., 2003), a brief, 28-item retrospective self-report measure of the frequency of abuse and neglect experienced prior to age 18 years; (4) the Children's Depression Inventory (CDI, Kovacs, 1985), a brief 27-item self-report measure that assesses the amount and severity of depressive symptoms in children and adolescents (Kovacs, 1985), and (5) the Adolescent Drinking Inventory (ADI, Harrell, Sowder, & Kapsak, 1988), a brief 24-item screening instrument used to assess alcohol-related drinking problems in adolescents (Harrell & Wirtz, 1989; McPherson & Hersch, 2000). Full-scale IQ was determined using the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999) two-subset form consisting of the Vocabulary and Matrix Reasoning subtests. In addition, all participants underwent a general physical examination.

Emotion processing task

The fMRI task, which has previously been described (Van Buuren, Vink, Rapcencu, & Kahn, 2011; Vink et al., 2014), consists of the presentation of colour images from the IAPS (Bradley, Greenwald, Petry, & Lang, 1992; Lang et al., 1997). The images, which depict animals, household objects, human facial expressions, weapons, and outdoor scenes, amongst others (Bradley et al., 1992), were categorized, as per validated ratings of the IAPS, into three conditions (i.e. neutral, positive, and negative). Each of the conditions contained 32 images. Valence and arousal ratings [mean, (*SD*)] of images (Libkuman, Otani, Kern, Viger, & Novak, 2007) viewed in each condition were respectively: 5.01 (0.32) and 2.76 (0.49) for the neutral images, 7.58 (0.42) and 5.64 (0.82) for the positive images, and 2.32 (0.52) and 5.91 (0.80) for the negative images. Valence scores for each condition (i.e. neutral, positive and negative) differed significantly from each other, with negative pictures being further from neutral trials than positive trials ($p < 0.01$). In terms of arousal scores, the positive and negative conditions differed significantly from the neutral condition ($p < 0.01$), with no significant difference in arousal evident between the negative and positive conditions ($p > 0.05$).

Task instructions were provided to participants during a training session prior to the neuroimaging assessment. Participants were instructed to view each image presented on the screen (2 s), after which the words 'negative, neutral, positive' appeared on the screen. Thereafter, participants were required to rate the image (i.e. negative, neutral, or positive) by pressing a button on a control panel (maximum of 2 s). The task contained four experimental activation blocks (96 s) interleaved with four baseline rest block (attending to a fixation cross,

32 s). Eight images of each condition were presented in a pseudo-random order, within each of the activation blocks. Each activation block consisted of 24 images. A fixation cross appeared for the remaining trial duration, after each response (Van Buuren et al., 2011; Vink et al., 2014).

Image acquisition

Imaging data were acquired on a 3T Siemens Allegra MR, with a four channel head coil. Scanning took place at the Combined Universities Brain Imaging Centre (CUBIC) at the Stellenbosch University Medicine and Health Sciences Campus, Tygerberg Medical School, Cape Town, South Africa. 622 whole-brain 2D-EPI images (TR = 1600 ms, TE = 23 ms, flip-angle: 72.5 degrees, FOV: 256x256, 30 slices, 4mm isotropic voxels) were acquired in about 16 mins. For image registration, a T1 ME-MPRAGE weighted structural scan was acquired (TR = 2530 ms; TE₁ = 1.53 ms TE₂ = 3.21 ms, TE₃ = 4.89 ms, TE₄ = 6.57 ms, flip-angle: 7 degrees, FOV: 256 mm, 128 slices, 1 isotropic voxel size) (van der Kouwe, Benner, Salat, & Fischl, 2008).

Image pre-processing

Images were analyzed using SPM12 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). Pre-processing and first-level statistical analysis was undertaken as previously described (Hoogendam et al., 2013). In brief, pre-processing involved correction for slice timing differences, re-alignment to correct for head motion, spatial normalization to the Montreal Neurological Institute template brain, and spatial smoothing to accommodate inter-individual differences in neuro-anatomy. Head motion parameters were analysed to ensure that the maximum motion did not exceed a predefined threshold (scan-to-scan > 3 mm) (van Dijk, Sabuncu, & Buckner, 2012).

First-level analysis

The first-level analysis is the same as that described by both Van Buuren et al. (2001) and Vink et al. (2014). General linear modelling was utilized to assess the effects of the three IAPS conditions (i.e. neutral, negative and positive) on brain activation in each individual. Only trials which were accurately matched in accordance with the IAPS categorization ratings were allocated to a condition and included in the analyses. Subsequently, the design matrix of the

regression model included three factors which modelled both the onsets and duration of the matching neutral, negative and positive trials, as well as a factor modelling both the onsets and duration of non-matching trials. All factors were convolved with a canonical hemodynamic response function. The design matrix included six realignment parameters (regressors of no interest) so as to correct for head motion. The data were subject to a high-pass filter, with a frequency of 0.0058 Hz so as to correct for low-frequency drifts in the signal. Thereafter, first-level contrast images were created for each participant (i.e. negative condition vs. neutral condition, positive condition vs. the neutral condition, and neutral condition vs. baseline).

Region of interest analysis

In order to assess brain activation in response to emotionally arousing images (i.e. negative and positive images vs. neutral images), regions of interest (ROI) analyses were performed within a priori determined ROIs, namely, bilateral amygdala, bilateral hippocampus, and bilateral insula. These ROIs were created based on their definition in the Anatomical Automatic Labeling atlas (AAL atlas, Tzourio-Mazoyer et al., 2002). See Figure 1(a) to (c) indicating the three ROIs created using the AAL atlas (Tzourio-Mazoyer et al., 2002). The mean regression coefficient (*b*-value) over all voxels per ROI was calculated for negative vs. neutral condition and positive vs. neutral condition, for each participant.

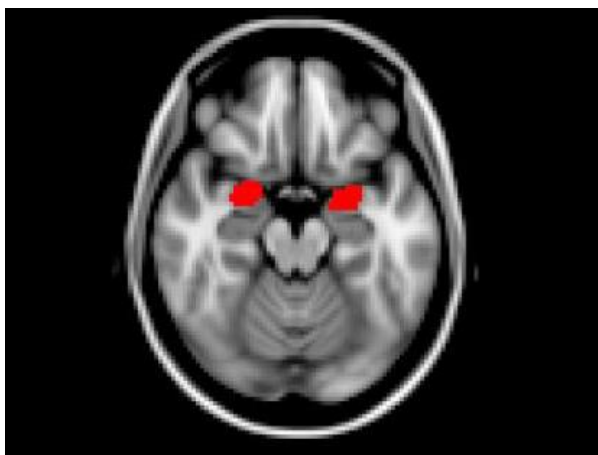


Figure 1(a): Indicates bilateral amygdala created using the AAL atlas (Tzourio-Mazoyer et al., 2002).

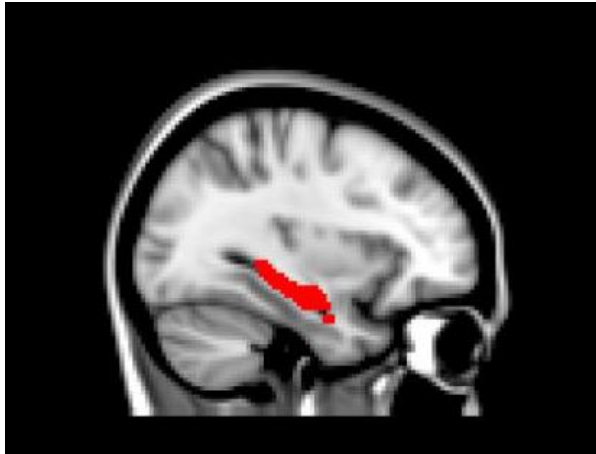


Figure 1(b): Indicates the hippocampus created using the AAL atlas (Tzourio-Mazoyer et al., 2002).

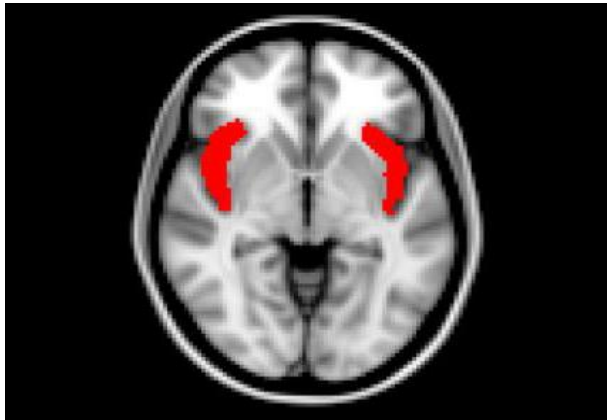


Figure 1(c): Indicates bilateral insula created using the AAL atlas (Tzourio-Mazoyer et al., 2002).

Data analysis

Univariate normality was determined for all demographic and clinical variables. To determine whether there were group differences (i.e. low CM - low AP, low CM - high AP, high CM - low AP, and high CM - high AP) in demographic [i.e. age, gender, grade at school, attending school, ethnicity, and socio-economic status (SES)] and clinical [i.e. CM, AP, depression, alcohol use, IQ, and change in score from pre-scan state anxiety to during scan state anxiety] variables, chi-square tests for categorical variables and one-way analysis of variance (ANOVA) tests for continuous variables, were employed. If group differences were present, one-way ANOVAs were employed to assess the effects of potential categorical covariates (e.g.

ethnicity) on functional neuroimaging behavioural and activation outcomes. Pearson's correlation statistic was used to determine whether there were significant associations between potential continuous covariates (e.g. self-reported depression score) and fMRI behavioural and activation outcomes.

In terms of IAPS task performance (i.e. reaction time and image matching accuracy), means were computed for the three conditions (i.e. neutral, negative, and positive), for the total sample and across the four groups. Thereafter, two-way ANOVAS were employed to determine the main effects of CM, AP, as well as the interaction effects of CM and AP on task performance. Cohen's *d* was calculated to provide an indication of the effect size of significant results or results that were trending to significance. Pearson's correlation statistic was used to determine if there were any significant associations between (1) task performance outcomes in the total sample as well as in change scores (i.e. negative and positive vs. neutral reaction time and accuracy differences) and (2) CM and AP total scores.

Mixed model repeated measures analysis of variance (ANOVA) tests were used to assess for any significant main effects of task contrasts (i.e. activation evident in 3 ROIs to viewing neutral vs. negative and positive images in the sample overall) or any significant interaction effects (i.e. CM x task contrast, AP x task contrast, and CM x AP x task contrast). Two-way ANOVAs were used to determine if there were any significant main effects (i.e. CM and AP) or interaction effect (i.e. CM x AP) on change scores (i.e. BOLD response to negative > BOLD response to neutral, and BOLD response positive > BOLD response neutral) in the 3 ROIs. Associated arithmetic means for the four groups in terms of BOLD response change scores were determined. Pearson's correlation statistic was used to determine if there were any significant associations between CM and AP total scores and change scores (i.e. negative > neutral, and positive > neutral).

In cases where Levene's test of homogeneity was significant at the 0.01 level ($p < 0.01$), both LS means and weighted means were inspected. Fisher's LSD post-hoc test results or Games-Howell post-hoc test results (i.e. if Levene's test of homogeneity was significant at the 0.01 level) were reported. Statistical significance was set at $p < 0.05$.

Results

Demographic and clinical characteristics of the study sample (n=78)

The 2nd tier sample consisted of 111 right-handed healthy adolescents, of which 99 underwent fMRI. The mean age of the participants was 16.99 years ($SD = 0.93$, range: 15 to 18). See Table 1. The sample was predominantly female (56/78, 71.8%). The majority (70/78, 90%) were attending school at the time of their participation [mean grade: 11 ($SD = 1.00$), range: grades 9 to 12]. Adolescents who were not in school had either completed grade 12 (7/78, 9%) or had dropped out of school (1/78, 1.3%). The majority of the sample self-identified as Black (60/78, 76.9%), followed by mixed race (17/78, 21.8%), and ‘other’ (1/78, 1.3%). 6.41% (5/78) of the sample met criteria for past major depressive episode, with no other current or past psychiatric disorder(s) evident.

Of the n=99 who underwent fMRI, n=21 were excluded due to either low (i.e. below 100) signal to noise ratio or excessive head motion [$> 3\text{mm}$ (van Dijk et al., 2012)]. This loss rate of approximately 21% is typically reported in neuroimaging studies conducted in children and adolescents (Yerys et al., 2009). A significant correlation was evident between AP total score and mean head motion during scanning ($r=0.23$, $p<0.05$) but not between CM total score and mean head motion during scanning ($r=0.17$, $p>0.05$).

As indicated in Table 1, there were no significant differences across the four groups in terms of age, gender, current grade at school, school attendance status, SES, alcohol use, IQ score or state anxiety change score (i.e. from pre-scan to during scan). Group differences were present for ethnicity [$X^2(3)=10.39$, $p<0.05$] and self-reported depression [$F(3, 74)=3.95$, $p<0.01$]. There were more Black participants than mixed race participants in the high AP groups than in the low AP groups, and participants in the high AP groups reported more depression symptoms than those in the low AP groups. Correlation analyses between self-reported depression scores and variables of interest (i.e. brain activation in ROIs in response to viewing neutral, negative and positive images; change scores in activation in terms of negative $>$ neutral and positive $>$ neutral; and behavioural data) indicated a few correlations below 0.30, which would not significantly influence results. One-way ANOVAs revealed no significant differences between Black and mixed race participants on any functional activation variables, however, significant

ethnicity effects were evident for a number of behavioural parameters. Ethnicity was therefore included as a covariate in the behavioural analyses only.

Table 1

Demographic and clinical characteristics of the total sample and by group (n=78).

Variable	Description	low CM-low AP (n=25) (M, SD)	low CM-high AP (n=20) (M, SD)	high CM-low AP (n=15) (M, SD)	high CM-high AP (n=18) (M, SD)	p-value
Age		16.96 (0.98)	16.75 (1.02)	17.33 (0.62)	17.00 (0.97)	<i>n.s.</i>
Gender	Male	9	4	5	4	<i>n.s.</i>
	Female	16	16	10	14	
Grade		10.90 (0.89)	11.00 (1.03)	10.58 (1.16)	10.58 (1.00)	<i>n.s.</i>
Attending school	Yes	21	20	12	17	<i>n.s.</i>
	Completed	4	0	2	1	
	Dropped out	0	0	1	0	
Ethnicity	Black	15	19	10	16	<0.05
	Mixed race	10	1	4	2	
	Other	0	0	1	0	
SES		12.80 (2.53)	11.10 (2.43)	11.47 (2.29)	11.33 (2.06)	<i>n.s.</i>
CM	CTQ	29.52 (3.18)	30.45 (3.38)	57.33 (6.45)	66.11 (11.86)	<0.01

Variable	Description	low CM-low AP (n=25) (M, SD)	low CM-high AP (n=20) (M, SD)	high CM-low AP (n=15) (M, SD)	high CM-high AP (n=18) (M, SD)	p-value
AP	TA and AS	66.44 (8.69)	86.25 (7.78)	67.40 (6.30)	85.94 (9.41)	<0.01
Depression	CDI	4.40 (3.67)	10.35 (5.58)	5.80 (3.80)	13.22 (6.98)	<0.01
Alcohol use	ADI	6.60 (7.38)	5.70 (5.17)	3.67 (4.72)	5.06 (5.90)	n.s.
IQ	WASI	3.17 (7.22)	-0.09 (4.11)	-2.80 (8.86)	-0.53 (7.27)	n.s.
State anx change	STAI-S	-2.32 (9.27)	-3.47 (17.01)	0.47 (13.18)	-2.67 (15.65)	n.s.

Note: CM = childhood maltreatment; CTQ = Childhood Trauma Questionnaire; AP = anxiety proneness; SES = socio-economic status; STAI-T = trait anxiety; AS = anxiety sensitivity; CDI = Child Depression Inventory; MASC = Multidimensional Anxiety Scale for Children; ADI = Adolescent Drinking Inventory; STAI-S = state anxiety; IQ scores are standardised scores; State anx change = change in state anxiety from pre-scan to during scan.

Task-dependent behaviour

See Table 2 for behavioural results (i.e. reaction times and image matching accuracy) for the total sample. According to the validated IAPS ratings, on average, participants rated negative images with the most accuracy (82.87%), followed by neutral images (68.59%) and positive images (57.59%). Given that the task was relatively simple and cognitive demands were low, the low accuracy rate determined for neutral and positive images was unexpected, and not consistent with higher accuracy levels for all images determined previously in non-clinical adolescents (Vink et al., 2014). No significant associations were evident between both CM total score or AP total score and any of the behavioural performance indicators across the total sample ($p>0.05$). No significant group differences were found for matching accuracy or reaction times ($p>0.05$). See Table 3.

ANCOVA (i.e. controlling for ethnicity) revealed no significant main (i.e. CM, AP) or interaction effects (i.e. CM x AP) on either reaction time or image matching accuracy ($p>0.05$).

Table 2

IAPS task performance and correlations between childhood maltreatment and anxiety proneness total scores and task performance.

Performance indicators	Condition	Overall performance	CTQ score (r, p)	AP score (r, p)
Reaction time in ms (<i>SE</i>)	Neutral	509.76 (19.82)	0.002 (0.99)	0.034 (0.77)
	Negative	504.95 (18.96)	-0.021 (0.86)	0.062 (0.59)
	Positive	521.02 (19.91)	0.036 (0.76)	0.035 (0.76)
	Neutral to negative	-4.80 (69.20)	-0.054 (0.64)	0.050 (0.66)
	Neutral to positive	11.30 (84.91)	0.068 (0.56)	0.002 (0.98)
Image matching accuracy in % (<i>SE</i>)	Neutral	68.59 (2.49)	-0.188 (0.10)	-0.093 (0.42)
	Negative	82.87 (1.74)	-0.080 (0.49)	0.081 (0.48)
	Positive	57.59 (2.23)	-0.149 (0.19)	-0.032 (0.78)
	Neutral to negative	14.29 (22.27)	-0.130 (0.26)	-0.147 (0.20)
	Neutral to positive	-10.99 (27.41)	-0.043 (0.71)	-0.051 (0.66)

Note: CTQ = Childhood Trauma Questionnaire; AP = anxiety proneness; ms = milliseconds.

Table 3

Reaction time and image matching accuracy change scores across groups.

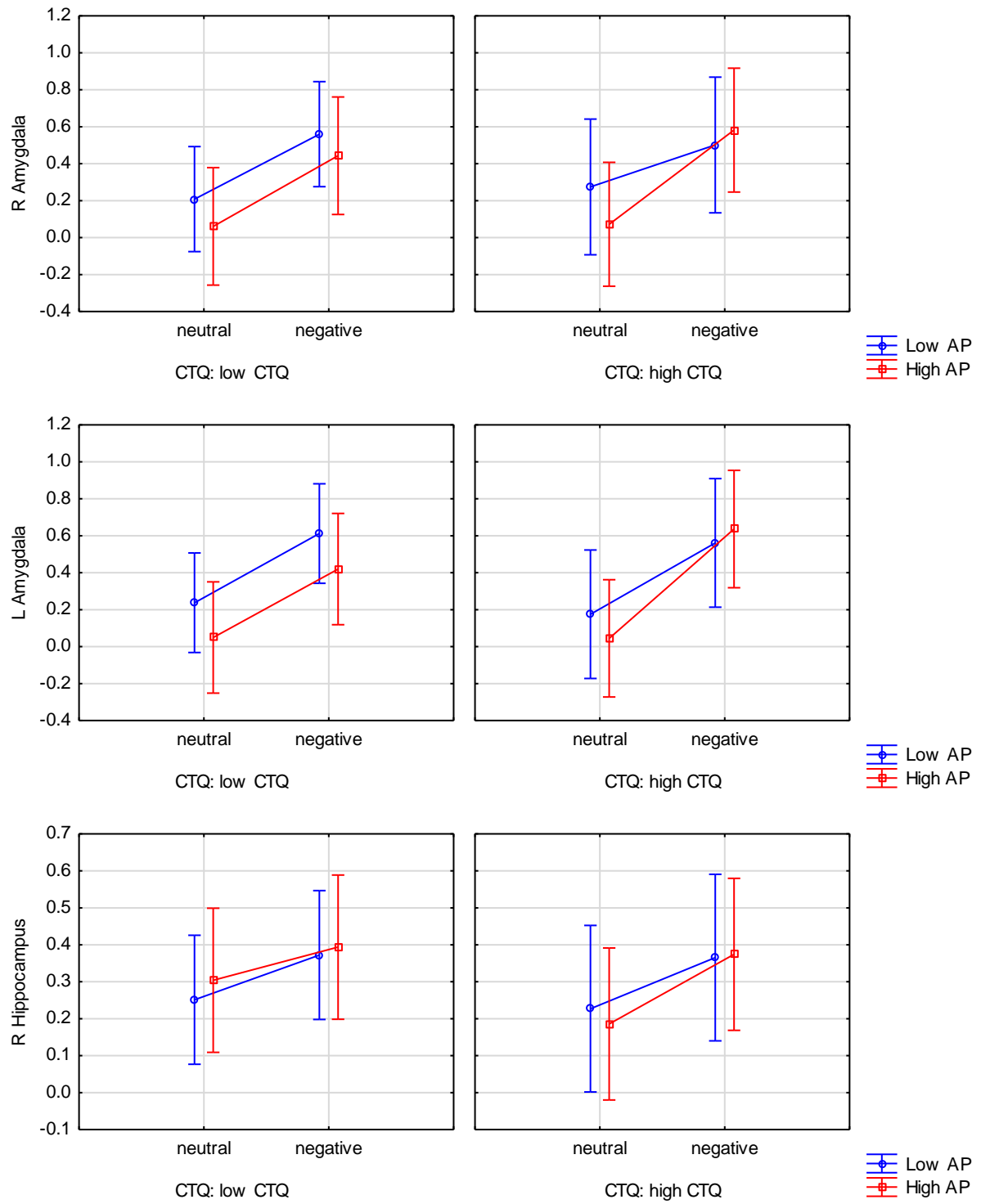
Behavioural measure	low CM-low AP (M, SE)	low CM-high AP (M, SE)	high CM-low AP (M, SE)	high CM-high AP (M, SE)	<i>p</i> -value
RT neutral to negative match (ms)	-10.76 (15.42)	12.13 (18.14)	-11.68 (12.44)	-10.02 (14.05)	<i>n.s.</i>
RT neutral to positive match	-3.90 (20.56)	10.44 (19.77)	29.64 (22.34)	18.91 (11.90)	<i>n.s.</i>
ACC neutral to negative match (%)	9.00 (4.26)	17.50 (5.90)	11.61 (4.29)	20.14 (5.29)	<i>n.s.</i>
ACC neutral to positive match	-11.25 (5.42)	-9.38 (7.10)	-16.07 (6.18)	-8.51 (6.48)	<i>n.s.</i>

Note: CM = childhood maltreatment; AP = anxiety proneness; RT = reaction time; ms = milliseconds; ACC = accuracy rate; *n.s.* = non-significant *p*-value.

Imaging

Task contrasts: (1) neutral vs. negative and (2) neutral vs. positive

A significant main effect of ‘task contrasts’ in terms of neutral vs. negative contrast was evident across the total sample in bilateral amygdala [Left: $F(1,74)=72.56$, $p<0.01$, $d=0.64$; Right: $F(1,74)=72.04$, $p<0.01$, $d=0.53$] and bilateral hippocampus [Left: $F(1,74)=22.62$, $p<0.01$, $d=0.31$; Right: $F(1,74)=20.50$, $p<0.01$, $d=0.31$], but not insula ($p>0.05$). See Figure 2. Similarly, a significant main effect of ‘task contrasts’ in terms of neutral vs. positive contrast was evident across the total sample in bilateral amygdala [Left: $F(1,74)=23.99$, $p<0.01$, $d=0.42$; Right: $F(1,74)=15.53$, $p<0.01$, $d=0.33$] and bilateral hippocampus [Left: $F(1,74)=11.17$, $p<0.01$, $d=0.27$; Right: $F(1,74)=4.84$, $p<0.05$, $d=0.19$], but not insula ($p>0.05$). See Figure 3. No significant interaction effects (i.e. CM x emotion, AP x emotion, and CM x AP x emotion) were evident ($p>0.05$).



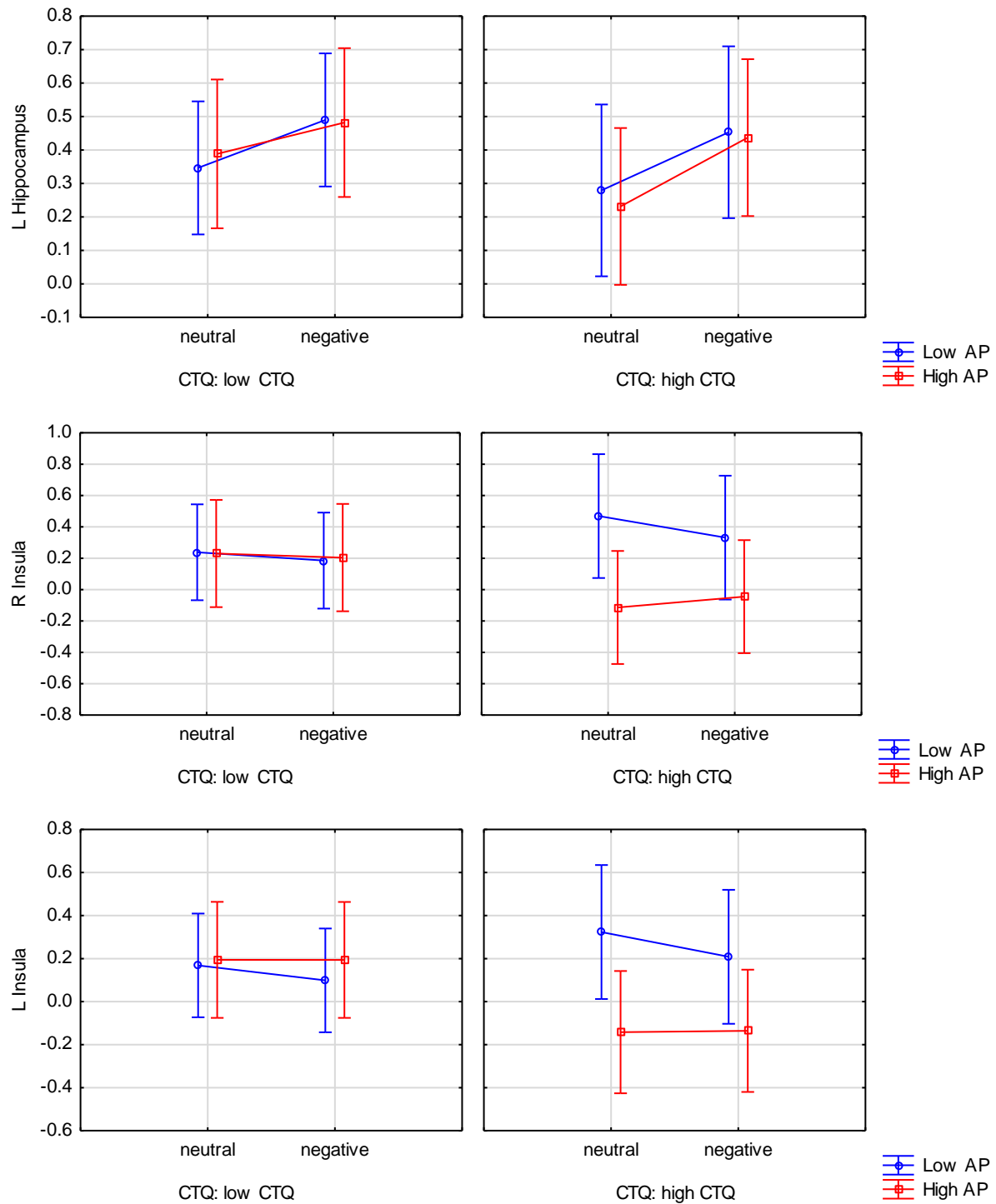
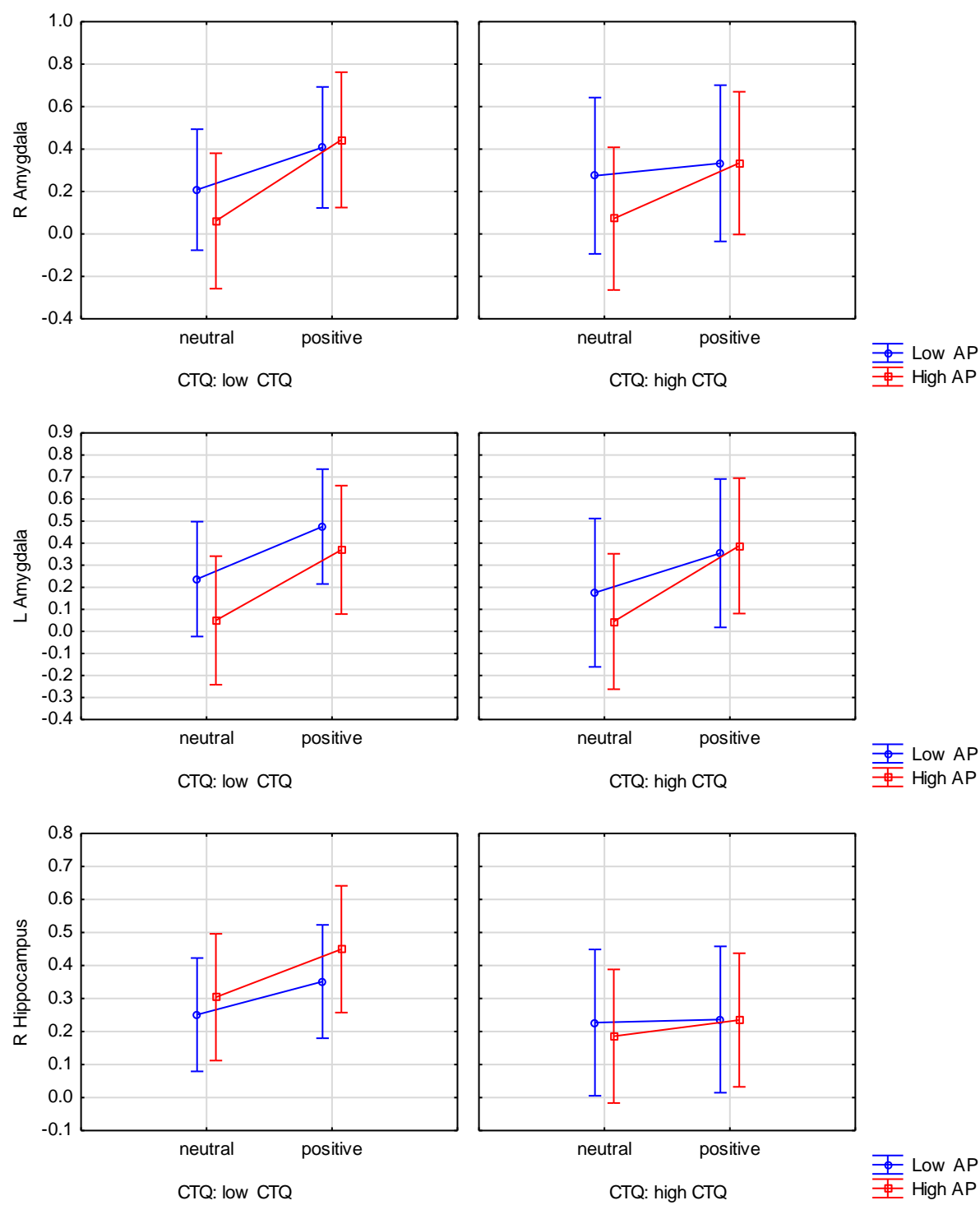


Figure 2: Indicates the main effect of task contrast (neutral to negative image), in the total sample, by childhood maltreatment level (i.e. CTQ low and high) and anxiety proneness level (i.e. low and high), on bilateral amygdala ($p < 0.01$) and hippocampus ($p < 0.01$). No main effect on bilateral insula was evident ($p > 0.05$).



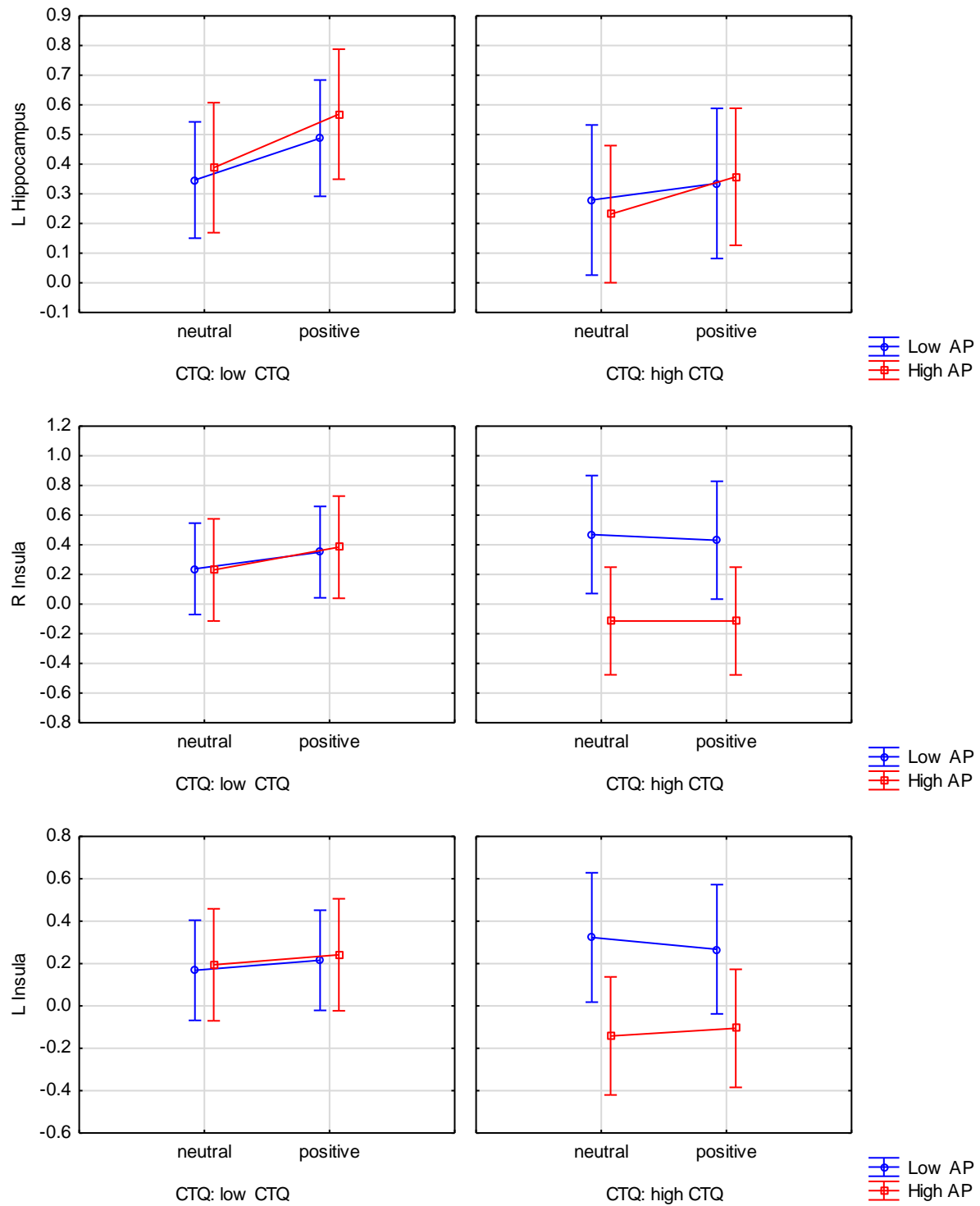


Figure 3: Indicates the main effect of task contrast (neutral to positive image), in the total sample, by childhood maltreatment level (i.e. CTQ low and high) and anxiety proneness level (i.e. low and high), on bilateral amygdala ($p < 0.01$) and hippocampus ($p < 0.05$). No main effect on bilateral insula was evident ($p > 0.05$).

Change scores: (1) negative > neutral and (2) positive > neutral

No significant main (i.e. CM or AP) or interaction effects (i.e. CM x AP) on BOLD response change were found between neutral and negative activation, and between neutral and positive activation, in any of the 3 ROIs ($p > 0.05$). A trend for a main effect of AP ($p = 0.07$, $d = 0.37$) was evident in the right amygdala in response to viewing and correctly matching negative images, with the high AP group tending to demonstrate greater activation in the right amygdala than the low AP group [$M = 0.446$ ($SE = 0.61$) vs. $M = 0.289$ ($SE = 0.06$)]. Similarly, a trend for a main effect of AP ($p = 0.09$, $d = 0.37$) was evident in the right amygdala in response to viewing and correctly matching positive images, with the high AP group tending to demonstrate greater activation in the right amygdala than the low AP group [$M = 0.322$ ($SE = 0.08$) vs. $M = 0.129$ ($SE = 0.08$)]. No such trends were evident in the hippocampus or insula for either change scores. Furthermore, no significant group differences ($p > 0.05$) were evident in terms of either change scores. See Table 4. Neither CTQ total score nor AP total score correlated significantly with either of the change scores ($p > 0.05$).

Table 4

Group comparison of brain activity response by task contrasts (negative and positive activation greater than neutral).

Region	Side	Contrast	low CM-low AP (n=25) (M, SE)	low CM-high AP (n=20) (M, SE)	high CM-low AP (n=15) (M, SE)	high CM-high AP (n=18) (M, SE)	<i>p</i> -value
Amygdala	L	negative > neutral	0.375 (0.06)	0.370 (0.14)	0.386 (0.09)	0.592 (0.09)	<i>n.s.</i>
	R	negative > neutral	0.351 (0.07)	0.382 (0.10)	0.227 (0.06)	0.510 (0.09)	<i>n.s.</i>
	L	positive > neutral	0.238 (0.09)	0.320 (0.09)	0.179 (0.11)	0.343 (0.14)	<i>n.s.</i>
	R	positive > neutral	0.199 (0.07)	0.382 (0.09)	0.059 (0.11)	0.262 (0.17)	<i>n.s.</i>
Hippocampus	L	negative > neutral	0.143 (0.06)	0.094 (0.08)	0.174 (0.05)	0.205 (0.05)	<i>n.s.</i>
	R	negative > neutral	0.121 (0.05)	0.090 (0.05)	0.138 (0.04)	0.188 (0.08)	<i>n.s.</i>
	L	positive > neutral	0.141 (0.06)	0.180 (0.10)	0.056 (0.07)	0.126 (0.06)	<i>n.s.</i>
	R	positive > neutral	0.100 (0.06)	0.146 (0.07)	0.009 (0.07)	0.049 (0.08)	<i>n.s.</i>
Insula	L	negative > neutral	-0.069 (0.08)	-0.000 (0.09)	-0.115 (0.11)	0.006 (0.07)	<i>n.s.</i>
	R	negative > neutral	-0.053 (0.11)	-0.026 (0.09)	-0.137 (0.12)	0.069 (0.09)	<i>n.s.</i>
	L	positive > neutral	-0.053 (0.11)	0.047 (0.09)	-0.056 (0.11)	0.036 (0.09)	<i>n.s.</i>
	R	positive > neutral	-0.053 (0.11)	0.154 (0.11)	-0.038 (0.73)	-0.000 (0.16)	<i>n.s.</i>

Note: CM = childhood maltreatment; AP = anxiety proneness; L = left; R = right; *n.s.* = non-significant *p*-value.

Discussion

To our knowledge, no studies to date have examined emotion processing in healthy adolescents with high and low levels of both CM and AP. The current study explored both the main and interaction effects of CM and AP on IAPS task performance (i.e. matching accuracy and reaction time) and brain activation during emotion processing in 3 ROIs (i.e. bilateral amygdala, bilateral hippocampus, and bilateral insula) in 78 right-handed, healthy, non-clinical adolescents categorised according to both high and low levels of CM and AP. In addition, the study aimed to elicit significant group differences in BOLD response.

The present study determined significant main effects of task contrasts (i.e. neutral vs. negative and neutral vs. positive emotion) in the sample overall, with significant increases in activation evident in both bilateral amygdala and bilateral hippocampus in response to viewing negative and positive images. Such findings are consistent with those determined in samples of healthy adolescent and adult samples where affect processing was assessed (Britton et al., 2006; Laeger et al., 2012; Mather et al., 2004; Sergerie, Chochol, & Armony, 2008; Vink et al., 2014). No significant main effects of task contrasts were observed in either left or right insula.

We found that neither CM nor AP had any statistically significant additive or interactive effects on neural responses to negative or positive images in the amygdala, hippocampus or insula in healthy adolescents. Additionally, no significant group differences in terms of neural responses in the three ROIs were observed. These findings suggest that neither the level of CM nor the level of AP, as categorised in this study, have differential impacts on emotion processing in adolescents. There may be a number of reasons for these findings. Firstly, in healthy participants, visual tasks using facial expressions of emotion to elicit emotional responses reportedly activate certain brain regions to a greater extent than tasks using images from the IAPS, including the insula (Britton et al., 2006). Indeed, previous studies have reported insula activation in response to facial expressions (i.e. particularly to expressions of sadness, anger, and disgust) in healthy, AP, and maltreated young adults (e.g. Fusar-Poli et al., 2009; Stein et al., 2007). Additionally, facial tasks depicting negative facial expressions elicit a significantly stronger BOLD response in the right amygdala, relative to negative IAPS images (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002). Negative IAPS images are also associated with significant habituation of the left amygdala, whereas negative facial expressions are associated with significant habituation of the right amygdala (Hariri, Tessitore, et al., 2002). Despite

images from the IAPS and facial tasks eliciting activation in similar structures (e.g. amygdala, hippocampus, ventromedial prefrontal cortex, and visual cortex), comparisons between these tasks across different samples is problematic, given that they elicit responses in different regions, specifically in the amygdala and insula, with these tasks thought to assess different aspects of emotion (i.e. recognition vs. direct emotion) (Britton et al., 2006). In addition, previous studies have reported that even simple rating tasks are associated with significantly less activation in the amygdala, not commonly seen under passive viewing conditions (Taylor et al., 2003). Given that the present study required participants to view and subsequently rate visual stimuli, such demands may have contributed to the non-significant findings. Furthermore, participants in this study were categorized into four groups based on specific cut-offs (i.e. 50th percentile of AP scores and 33rd and 66th percentile of their maltreatment scores). As groups size were relatively small, and low and high levels of AP were determined using the median split, there may have been limited statistical power to detect any significant effects. In addition, the cut-offs employed to determine high and low levels of CM were arbitrary and were not based on validated thresholds. Indeed, a previous study in adolescents in which images from the IAPS were employed to assess the effects of CM on emotion processing, employed validated cut-offs on the CTQ to determine the presence of abuse, as well as interviewed participants to assess their experiences with caregiving and abuse (McLaughlin et al., 2015). Another important finding from our study was the particularly poor matching accuracy for positive and neutral images (i.e. 57.6% for positive and 68.6% for neutral images). As we assessed functional outcomes and task-dependent behaviour on only correctly matched images, this may have further reduced statistical power in terms of the outcomes associated with task contrasts (e.g. positive > neutral).

The possibility of different underlying neural mechanisms associated with CM and AP, in the absence of clinical disorder, requires further investigation in this sample. Underlying neurobiological mechanisms in adolescents with CM-related disorders (e.g. childhood sexual abuse-related PTSD) have been shown to differ from that in adolescents with internalizing disorders, and relative to healthy controls, as evidenced by different habituation patterns of amygdala reactivity to salient stimuli (van den Bulk et al., 2016) despite the partial overlap in symptomatology (Lindert et al., 2014) and the similar neural patterns of increased amygdala activation to salient images.

Given the observed trends for greater right amygdala activation in response to negative ($p=0.07$) and positive images ($p=0.09$) in high AP adolescents, our findings tend to provide support for findings of increased amygdala reactivity to both negative and positive stimuli in AP youth and young adults characterized by high levels of anxiety-related traits such as trait anxiety and neuroticism (Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2011; Stein et al., 2007), as well as non-clinical individuals (Fusar-Poli et al., 2009; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001; Hamann, Ely, Hoffman, & Kilts, 2002; Laeger et al., 2012; Somerville, Kim, Johnstone, Alexander, & Whalen, 2004; Yang et al., 2002).

Our finding that levels of CM seemed to have no independent effect on neural responses to either negative or positive images in limbic structures is not consistent with studies that have assessed associations between childhood adversity (e.g. maltreatment, stressful life events) and enhanced amygdala (bilateral, right or left) reactivity and/or insula reactivity to viewing negative (Herrington et al., 2016; McLaughlin et al., 2015; Tottenham et al., 2011) and positive stimuli (Suzuki et al., 2014), as well as pre-attentively presented negative and positive stimuli (McCrory et al., 2013). That said, in a sample of youth, Suzuki and colleagues (2014) found that stressful life events (e.g. death of pet, new school, birth of sibling) were associated with increased amygdala activity to emotional faces (i.e. fearful, sad and happy faces), but no association between traumatic life events (e.g. physical and sexual abuse, motor vehicle accident, natural disaster) and amygdala reactivity to fearful faces, specifically, was determined. These results suggest that stressor severity may affect limbic responses to the type of emotion (e.g. fear, anger) and that youth with trauma histories may be desensitized to fearful or negative stimuli (Suzuki et al., 2014; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006). Furthermore, some studies in youth with early life adversity that have noted increased amygdala reactivity to positive and negative stimuli have included participants with and without psychopathology (e.g. McLaughlin et al., 2015; Tottenham et al., 2011) and despite controlling for such psychopathology, residual confounding may have played a role in these studies in which significant results were reported (McLaughlin et al., 2015).

In terms of task-dependent behaviour, neither CM nor AP had any significant main or combined effects on matching accuracy or reaction times. Furthermore, no significant differences in matching accuracy or reaction times were evident across the four groups. These findings suggest that adolescents characterised by high levels of both CM and AP performed equally well compared with the other three groups. Comparable task performance across

groups suggests that the task was relatively simple and that possible differences in neural activation across groups was not associated with variations in task performance (Hum, Manassis, & Lewis, 2013; Tottenham et al., 2011). In support of our findings, comparable task performance has been noted in samples of AP and anxiety-normative young adults, anxious and non-anxious youths and adults, trauma-exposed and non-exposed youths, and youth with and without early life adversity, using either the IAPS or facial tasks (Hum et al., 2013; Marusak, Martin, Etkin, & Thomason, 2014; McClure et al., 2007; McCrory et al., 2013; Shah, Klumpp, Angstadt, Nathan, & Phan, 2009; Simmons et al., 2011; Stein et al., 2007; Tottenham et al., 2011).

A number of study limitations should be taken into account in interpreting the current findings. First, the use of the 50th percentile to categorize participants as being high and low on AP may have reduced statistical power to detect an effect of AP on outcomes. Similarly, the cut-offs used to group participants as having high and low levels of CM were relatively arbitrary. Second, the sample consisted predominantly of female and Black adolescents and therefore our findings may not be generalizable to male adolescents or other ethnic groups. Third, the use of the CTQ, a retrospective, self-report measure of CM, may have introduced moderate recall bias which may have resulted in the over- or under-reporting of maltreatment frequency. Fourth, we did not assess the effects of particular childhood abuse and neglect types as our study was underpowered for such analyses.

Recommendations for future research include employing validated cut-points on self-report measures of CM to group participants on high and low levels of CM, as well as more stringent cut-offs to group participants on high and low AP (e.g. McLaughlin et al., 2015; Simmons et al., 2011; Surcinelli, Codispoti, Montebanocci, Rossi, & Baldaro, 2006). Furthermore, we recommend assessing the predictive potential of CM and AP, as well as their interaction, on emotion processing in adolescents. Such analysis will provide more statistical power to detect effects on emotion processing. Replication of the study in larger samples of adolescents categorised by abuse and neglect subtypes, is recommended, as it has been suggested that maltreatment type is associated with particular neurobiological changes (da Silva Ferreira, Crippa, & de Lima Osorio, 2014; Teicher & Samson, 2016). Age of onset of maltreatment, maltreatment duration, and severity of maltreatment, have been found to affect limbic reactivity to emotional stimuli (da Silva Ferreira et al., 2014; McCrory et al., 2013) and will therefore be useful to assess in future studies. In addition, given that previous studies have found

associations between higher levels of AP and increased amygdala reactivity in response to unattended and masked fear in healthy young adults (Dickie & Armony, 2008; Etkin et al., 2004), but no significant association between AP levels and activation in either the amygdala or hippocampus in response to non-masked fear (Etkin et al., 2004), future studies should assess the potential differential effects of masked vs. unmasked IAPS images on emotion processing outcomes in adolescents with varying levels of CM and AP. Finally, future studies assessing the effects of AP and CM on emotion processing may benefit from inclusion of functional connectivity analyses (i.e. between limbic subcortical structures and the prefrontal cortex) so as to provide a clearer understanding of regulatory responses associated with both CM and AP (Greening & Mitchell, 2015; Herringa et al., 2016; Kim et al., 2011).

In conclusion, our findings suggest that neither CM nor AP had any differential effects by level of severity on emotion processing. Regardless of levels of CM and AP, comparable results were determined across both functional activation outcomes and task dependent behaviour. The trend for greater activation in response to emotionally salient (i.e. negative and positive) images in the right amygdala evident in AP adolescents suggests that right amygdala hyperactivity may be a neural correlate of AP in healthy adolescents.

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CHAPTER 6

Gene-by-environment interaction of the BDNF *Val66Met* polymorphism and childhood maltreatment on anxiety proneness in a mixed race adolescent sample *(manuscript in preparation)*

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Short title: BDNF *Val66Met* in anxiety proneness

Abstract

Objectives: A gene-environment (G x E) interaction study was conducted to determine the interactive effect of the BDNF *Val66Met* polymorphism and childhood maltreatment (CM) to increase susceptibility to anxiety proneness (AP) in a sample of mixed race adolescents.

Methods: Participants (n=308, mean age: 15.8 years) who completed measures for AP and CM were genotyped for the BDNF *Val66Met* polymorphism. Multiple linear regression models were used to assess G x E influences on AP. Age and gender were included in the models as covariates.

Results: A main effect of CM on AP was evident, however, no main effect of BDNF genotype on AP was observed. There was a trend toward significance for a G x E effect on AP, with *Met66* allele carriers who endorsed high levels of CM, tending to have higher AP scores than *Val66* homozygotes ($p=0.06$).

Conclusions: Our results provide support for the moderating role of BDNF *Val66Met* in the relationship between early adversity and increased risk of anxiety-related phenotypes and anxiety disorder. Given the exploratory nature of this study, findings require replication in larger samples and adjustment for population stratification so as to confirm the role of BDNF *Val66Met* and CM on AP in mixed race adolescents.

Keywords: anxiety proneness, adolescents, genetics, gene-environment, BDNF *Val66Met*

Introduction

Anxiety disorders in youth are attributable to multiple causal mechanisms, comprising biological vulnerabilities, including genetics and temperament; and unfavourable environmental influences (Dabkowska & Dabkowska-Mika, 2015; Keeley & Storch, 2009; Weems & Stickle, 2005), such as childhood trauma (Dvir, Ford, Hill, & Frazier, 2014). Temperament or dispositional characteristics may be considered intermediate phenotypes for psychiatric disorders, reflecting sub-threshold clinical presentations (Altınbaş et al., 2015). Anxiety-related temperamental traits, such as anxiety sensitivity (AS) and trait anxiety (TA) (Eysenck, 1992; Reiss, Peterson, Gursky, & McNally, 1986) have consistently been found to be predictive of anxiety disorders and symptoms in youth (McLaughlin, Stewart, & Taylor, 2007; Muris, Schmidt, Merckelbach, & Schouten, 2001; Schmidt et al., 2010; Schmidt, Zvolensky, & Maner, 2006; Weems et al., 2007), particularly panic disorder symptoms (Hayward, Killen, Kraemer, & Taylor, 2000; Schmidt et al., 2006). Both AS and TA are considered developmentally stable risk factors for anxiety (Zavos, Gregory, et al. 2012; Zavos, Rijdsdijk, et al. 2012; Garcia et al. 2013). Where AS refers to fear of anxiety-related or arousal-related sensations and symptoms (Reiss & McNally, 1985) due to erroneous or dysfunctional beliefs about the consequences of such symptoms (Reiss et al., 1986), TA refers to the tendency to respond fearfully to stressors in general (McNally, 1989). Individuals with elevated levels of anxiety-related temperamental traits, such as those with high levels of AS or TA, may be termed ‘anxiety prone’ (AP), relative to those individuals with normative levels of anxiety (Simmons, Strigo, Matthews, Paulus, & Stein, 2006).

AS and TA are both moderately heritable, ranging between 34% and 45% for AS in youth and adults (Stein et al. 1999; Eley et al. 2007; Zavos et al. 2010), with similar rates of heritability reported for TA in children and adolescents (Legrand, McGue, & Iacono, 1999). AS is thought to be interactively impacted by additive genetic factors as well as unique environmental factors (Stein et al. 1999; Garcia et al. 2013), such as stressful life events (Aktekin et al. 2001; Zavos, Wong, et al. 2012), including childhood maltreatment (CM) and severe family conflict (McLaughlin & Hatzenbuehler, 2009; Scher & Stein, 2003), demonstrating the interactive effect of genes and environment on AP.

Brain-derived neurotrophic factor (BDNF) is a secretory protein in the neurotrophin family known to influence the proliferation, survival, differentiation, repair, and regulation of synaptic

plasticity of neuronal cells in the developing and adult brain (Bath & Lee, 2006; Chen et al., 2006; Martinowich, Manji, & Lu, 2007; Notaras, Hill, & van den Buuse, 2015). BDNF is widely expressed in the hippocampus and cerebral cortex (Hofer, Pagliusi, Hohn, Leibrock, & Barde, 1990; Huang & Reichardt, 2001) and enhances hippocampal long-term potentiation (Figurov, Pozzo-Miller, Olafsson, Wang, & Lu, 1996) associated with both memory and learning efficiency (Hariri et al., 2003; Yamada, Mizuno, & Nabeshima, 2002). The gene encoding BDNF contains a functional single-nucleotide polymorphism (SNP) resulting in a valine (val) to methionine (met) substitution at amino acid 66 (*Val66Met*, rs6265) in the 5' pro-BDNF domain (Egan et al., 2003). Compared with the *Val66* allele, the *Met66* allele is associated with a decrease in activity-dependent secretion of BDNF (Egan et al., 2003). BDNF has received attention due to its evident role in anxiety and mood disorders (Angelucci et al., 2014; Hemmings et al., 2008; Li, Chang, & Xiao, 2016; Martinowich et al., 2007; Molendijk et al., 2014; Suliman, Hemmings, & Seedat, 2013), although findings have been inconsistent across studies (Frustaci, Pozzi, Gianfagna, Manzoli, & Boccia, 2008; Hong, Liou, & Tsai, 2012; Lam, Cheng, Hong, & Tsai, 2004; Minelli et al., 2011; Notaras et al., 2015; Surtees et al., 2007; Wang et al., 2015).

Some studies have found the BDNF *Val66Met* polymorphism to be associated with personality traits such as TA and neuroticism (Lang et al., 2005; Sen et al., 2003), while others have not (Terracciano et al., 2010; Willis-Owen et al., 2005). Previous studies have found associations between the *Met66* allele and increased introversion (Terracciano et al., 2010), harm avoidance (Montag, Basten, Stelzel, Fiebach, & Reuter, 2010), and tendency to ruminate (Beevers, Wells, & McGeary, 2009), lower levels of conscientiousness (Hiio et al., 2011), an increased vulnerability to stress (Casey et al., 2009), increased anxiety-related behaviours (Chen et al., 2006), and increased risk of an anxiety disorder in children and adolescents (Tocchetto et al., 2011). In contrast, other studies have reported an association between the *Val66* allele and higher neuroticism scores, as well as increased risk of anxiety symptoms during adolescence (Chen, Yu, Liu, Zhang, & Zhang, 2015; Frustaci et al., 2008).

Studies have demonstrated that acute and chronic stress (e.g. military training, psychological job stress, acute and repeated restraint in animals) are associated with decreased BDNF (Mitoma et al., 2008; Murakami, Imbe, Morikawa, Kubo, & Senba, 2005; Suzuki et al., 2014) and enhancement of anxiety-related behaviours (Chen et al., 2006). In adults with lifetime major depressive disorder, for example, a linear relationship between exposure to childhood

trauma (i.e. emotional neglect, psychological abuse, and sexual abuse) and reduced BDNF serum levels has been demonstrated in *Met66* allele carriers, with the lowest BDNF levels evident in *Met66* carriers reporting two or more childhood trauma types (Elzinga et al., 2011). Similarly, compared with non-trauma exposed children and adolescents, youth with CM histories (i.e. sexual abuse) have been found to exhibit significantly lower serum BDNF levels, with the lowest levels documented in those with multiple sexual assault histories (Şimşek, Yüksel, Kaplan, Uysal, & Alaca, 2015).

There is support for the role of gene-environment interaction in the aetiology of youth and adult anxiety, including panic and separation anxiety, anxiety symptoms, anxious mood, TA, and AS (Baumann et al., 2013; Chen et al., 2015; Gunthert et al., 2007; Ibarra et al., 2014; Klauke et al., 2011; Lau, Gregory, Goldwin, Pine, & Eley, 2007; Stein, Schork, & Gelernter, 2008; Vendliniski, Lemery-Chalfant, Essex, & Goldsmith, 2011). CM and AP have both consistently been implicated as risk factors for psychopathology, including anxiety disorders (Collishaw et al. 2007; McLaughlin et al. 2007; Kessler, McLaughlin, et al. 2010; McLaughlin et al. 2012). We have previously determined, in a sample of secondary school-attending adolescents, that CM is significantly and positively associated with AP (Martin, Viljoen, Kidd, & Seedat, 2014). Further, there is evidence for a moderating role of BDNF *Val66Met* in the relationship between life stress, including abuse and neglect, and subsequent risk for psychopathology (e.g. depression) in youth and adults (Carver, Johnson, Joormann, Lemoult, & Cuccaro, 2011; Chen, Li, & McGue, 2013; Gutiérrez et al., 2015; Hosang, Shiles, Tansey, McGuffin, & Uher, 2014). G x E interactions (i.e. BDNF *Val66Met* and early life stress exposure) have previously been found to be associated with abnormalities in brain structures, physiological indicators, deficits in cognition (i.e. poorer working memory), higher levels of depression and anxiety, and elevated temperamental traits (Gatt et al., 2009). To our knowledge, no previous studies have investigated whether the BDNF *Val66Met* polymorphism interacts with CM to increase susceptibility to AP. In addition, relative to studies that have assessed the BDNF *Val66Met* polymorphism in Caucasian samples, there is limited information of the allelic distribution of the BDNF *Val66Met* polymorphism in South African samples, particularly ethnically diverse samples. A G x E interaction study was conducted to determine the interactive effect of the BDNF *Val66Met* polymorphism and CM to increase susceptibility to AP in a sample of mixed race adolescents.

Materials and methods

Design

This study was a two-tier study in a sample of secondary school students. Tier 1 employed stratified two-stage cluster sampling in which public secondary schools in Cape Town, South Africa, and students within these schools, were randomly selected. The Tier 1 sample of secondary school students was therefore representative of students attending public secondary schools in Cape Town, South Africa. Tier 1 allowed for the screening (e.g. of levels of CM, AS and TA) and collection of salivary DNA from secondary school students from 29 public schools in Cape Town, South Africa. A description of tier 1 methods, including clinical data pertaining to Tier 1, has previously been reported (Martin, Kidd, & Seedat, 2016; Martin et al., 2014). Four groups of adolescents grouped according to levels of Tier 1 self-reported CM and AP, and matched as closely as possible on age, ethnicity, gender, and educational status, were included in the second tier of the study and underwent a neuropsychological and neuroimaging assessment, amongst others.

Participants

The Tier 1 sample consisted of 1149 secondary school students. DNA was extracted from 985 participants (i.e. comprising 85.7% of the total Tier 1 sample) at the same time that Tier 1 self-report measures (e.g. CM, AS, and TA) were administered. The majority of the Tier 1 sample consisted of Black (64.4%) and mixed race (32.2%) participants. As almost all Black participants (99.68%, 628/630) in the sample were *Val66Val* genotype carriers, the subset reported on here included only those participants that self-classified as ‘mixed race’ and for whom BDNF data were available (n=308).

This study was approved by the Health Research Ethics Committee of Stellenbosch University, South Africa (ethics reference number: N10/11/370), and permission to access secondary schools and conduct this study was provided by the Western Cape Education Department. Written informed consent was obtained from parents/legal guardians and written assent was obtained from the students themselves.

Self-report measures

The following self-report questionnaires were administered at the secondary schools on a single occasion:

(1) The *Childhood Anxiety Sensitivity Index* (CASI, Silverman, Fleisig, Rabian, & Peterson, 1991), an 18-item instrument that measures the fear of anxiety symptoms and is designed for use with school-age children and adolescents (Silverman et al., 1991).

(2) The trait version of the *State-Trait Anxiety Inventory* (STAI, Spielberger et al. 1983), a 20-item instrument that assesses an individual's predisposition to be anxious (Julian, 2011; Spielberger et al., 1983). Previous research that has compared high AP young adult students with lower AP young adult students (i.e. 18-21 year olds, grouped according to high and normative levels of TA as measured by the trait version of the STAI) found that the high AP group had significantly higher anxiety-related temperamental traits (i.e. AS, TA, and neuroticism) than did the low AP group (Stein, Simmons, Feinstein, & Paulus, 2007). In the current study, anxiety proneness (AP) was calculated by summing total CASI and STAI trait anxiety scores for each participant. The summing of CASI and STAI trait anxiety scores to calculate AP seemingly provides a more robust measure of AP than the analysis of independent CASI or STAI trait anxiety scores.

(3) The *Childhood Trauma Questionnaire – Short Form* (CTQ-SF, Bernstein et al. 2003), a brief, 28-item retrospective self-report measure of the frequency of abuse (i.e. emotional, physical, and sexual) and neglect (i.e. emotional and physical) experienced prior to age 18 years. The CTQ-SF yields a total score that can range from 25 to 125, with higher scores reflecting more severe levels of abuse or neglect. Scores for each of the CTQ-SF subscales can range from 5 to 25, with higher scores indicating more severe childhood trauma (Bernstein & Fink, 1998).

Genotyping

Genomic DNA was extracted from saliva collected in Oragene DNA self-collection kits (OG-500, DNA Genotek, Ontario, Canada) using the Prep-It L2P reagent (DNA Genotek) as per manufacturer's instructions. The BDNF *Val66Met* polymorphism (rs6265) was genotyped as previously described (Hemmings et al., 2008).

Statistical analysis

All analyses were conducted using STATISTICA version 13 (StatSoftInc.). Univariate normality was determined for all demographic and clinical variables. Demographic characteristics of the total sample (i.e. age, gender and current grade at school) were calculated as means (M) and standard deviations (SD s) for quantitative variables and counts and associated percentages for categorical variables (e.g. gender). The severity (i.e. minimal, moderate, severe, and extreme) of abuse and neglect categories of the CTQ (i.e. emotional, physical and sexual abuse; and emotional and physical neglect) were computed for the total sample using recommended cut-off scores (Bernstein & Fink, 1998).

To determine if AP levels differed by gender and age, t -tests and Pearson's correlation statistic, respectively, were employed.

Genotype counts (%) and the Hardy-Weinberg equilibrium (HWE) p -value was determined using the R Package SNPAssoc (González et al., 2007). The association between BDNF rs6265 and AP was assessed using a log-additive model [i.e. risk allele '0'=CC (i.e. *Val-Val*), '1'=CT (i.e. *Val-Met*), and '2'=TT (i.e. *Met-Met*)].

Demographic and clinical characteristics of the sample by genotype (i.e. *Val66* homozygotes and *Met66* allele carriers) were summarised as means (M 's) and standard deviations (SD 's) for quantitative variables, and counts were used for categorical variables. Independent samples t -tests and chi-square tests were used to determine any group (i.e. genotype) differences for the quantitative and categorical variables, respectively. Pearson's correlation statistic was used to assess the relationship between CTQ total score and AP total score by genotype.

Linear regression was used to assess the effects of BDNF genotype (i.e. coded as '0' for *Val66Val*, and '1' for *Met66* allele carriers), level of CM (CTQ total score), and the interaction of BDNF genotype and CM, on AP. In the first model, gender, age, BDNF genotype, and CTQ total score were included so as to assess the main effects of BDNF genotype and CTQ total score on the outcome, AP. In the second model, the two-way interaction term (i.e. BDNF x CTQ) was added. The F -to-remove test was used to compare the R^2 change between the first and second model to determine whether the inclusion of the interaction term resulted in a significant increase in explained variance.

Results

Demographic and clinical variables

All participants were secondary school students (mean grade: grade 10). The mean age of the sample was 15.8 years ($SD=1.59$). Over half the sample were female (183/308, 59.4%).

See Table 1 for frequencies and percentages of abuse and neglect types endorsed by the sample. Emotional abuse was the most frequently reported CM type (i.e. 57.4% of the sample reportedly experienced low to extreme forms of emotional abuse), followed by emotional neglect (i.e. 49.9% of the sample reportedly experienced low to extreme forms), and physical neglect (i.e. 43.8% low to extreme forms). Age was significantly associated with AP total score ($r=0.13$, $p<0.05$), and females had significantly higher AP scores than males [males: $M=73.69$, $SD=13.10$; females: $M=82.65$, $SD=14.23$, ($t(306)=-5.61$, $p<0.05$)].

Table 1

Frequencies and percentages of abuse and neglect categories in the total sample (n=308).

Childhood trauma category	None or minimal	Low to moderate	Moderate to severe	Severe to extreme
Emotional abuse	131 (42.5%)	87 (28.2%)	44 (14.3%)	46 (14.9%)
Physical abuse	211 (68.5%)	42 (13.6%)	23 (7.5%)	32 (10.4%)
Sexual abuse	202 (65.6%)	36 (11.7%)	39 (12.7%)	31 (10.1%)
Emotional neglect	154 (50%)	90 (29.2%)	38 (12.3%)	26 (8.4%)
Physical neglect	173 (56.2%)	61 (19.8%)	38 (12.3%)	36 (11.7%)

Genetic variables

The BDNF *Val66Met* SNP was in Hardy-Weinberg equilibrium ($p=0.456$). The following genotype frequencies were evident in our mixed race sample: *Val66Val* (75.65%, 233/308), *Val66Met* (22.08%, 68/308), and *Met66Met* (2.3%, 7/308). These frequencies are generally in line with those determined in Caucasian samples (Carver et al., 2011; Gatt et al., 2009; Pivac et al., 2009; Surtees et al., 2007; Zeni et al., 2013) and in South African mixed race samples (Dalvie et al., 2014), and confirm the low rates of *Met66* allele carriers evident in ethnic groups in Sub-Saharan Africa (Petryshen et al., 2009). Given the low frequency of *Met66Met* genotype carriers, *Val66Met* and *Met66Met* genotypes were combined (24.35%, 75/308) for genotypic analyses to increase statistical power. No significant differences in either demographic [i.e. age, and grade at school ($p>0.05$)] or clinical measures were evident ($p>0.05$). No association between gender and genotype was evident [χ^2 (1, N=308) = 0.480, $p>0.05$]. See Table 2 for demographic and clinical variables for by genotype.

Table 2

Summary statistics for demographic and clinical variables by BDNF genotype.

Variable	Genotype	N	Mean (SD)	p-value
Age	<i>Met66Met + Val66Met</i>	75	15.79 (1.71)	>0.05
	<i>Val66Val</i>	233	15.83 (1.56)	
Grade	<i>Met66Met + Val66Met</i>	75	9.98 (1.36)	>0.05
	<i>Val66Val</i>	231	9.86 (1.31)	
AP	<i>Met66Met + Val66Met</i>	75	79.31 (15.63)	>0.05
	<i>Val66Val</i>	233	78.92 (14.08)	
CTQ	<i>Met66Met + Val66Met</i>	75	42.36 (13.78)	>0.05
	<i>Val66Val</i>	233	44.18 (14.78)	

Abbreviations: AP, sum of anxiety sensitivity and trait anxiety; CTQ, Childhood Trauma Questionnaire.

Results of multiple regression analyses (i.e. model 1 and model 2) are presented in Table 3. A significant main effect of CM on AP was evident ($p < 0.01$), however, no significant main effect of BDNF genotype on AP was observed ($p > 0.05$). In the second model, although not statistically significant at the 0.5% level, a trend (i.e. $p = 0.06$) to a significant interaction effect was observed between BDNF *Met66* allele carriers (vs. *Val66* homozygotes) and CM on AP. The inclusion of the interaction term in the second model revealed an increase in explained variance at the 0.10 level ($p = 0.06$).

Table 3

Results of multiple linear regression analysis depicting main and interaction effects.

Model	Predictors	β	$t(p)$	R	R^2	ΔR^2	$\Delta F(p)$
1	Gender	0.29	6.14*	0.577	0.332		
	Age	0.10	2.22*				
	BDNF <i>Met66</i>	0.05	1.05				
	CTQ	0.47	10.05*				
2	Gender	0.28	6.05*	0.583	0.340	0.008	3.479 (0.06)
	Age	0.10	2.19*				
	BDNF <i>Met66</i>	-0.22	-0.22				
	CTQ	0.43	8.08*				
	BDNF <i>Met66</i> x CTQ	0.28	1.87 (0.06)				

Abbreviations: BDNF *Met66*, BDNF *Met66* allele carriers vs. BDNF *Val66* homozygotes; CTQ, Childhood Trauma Questionnaire; β , standardized regression coefficient; $t(p)$, t -statistic and associated p -value; * $p < 0.05$; R , correlation statistic; R^2 , explained variance.

Associations between BDNF genotype, CTQ total score and AP are depicted in Figure 1. As indicated, the correlation between CTQ and AP was relatively stronger in *Met66* allele carriers ($r = 0.60$, $p < 0.01$) than in *Val66* homozygotes ($r = 0.45$, $p < 0.01$).

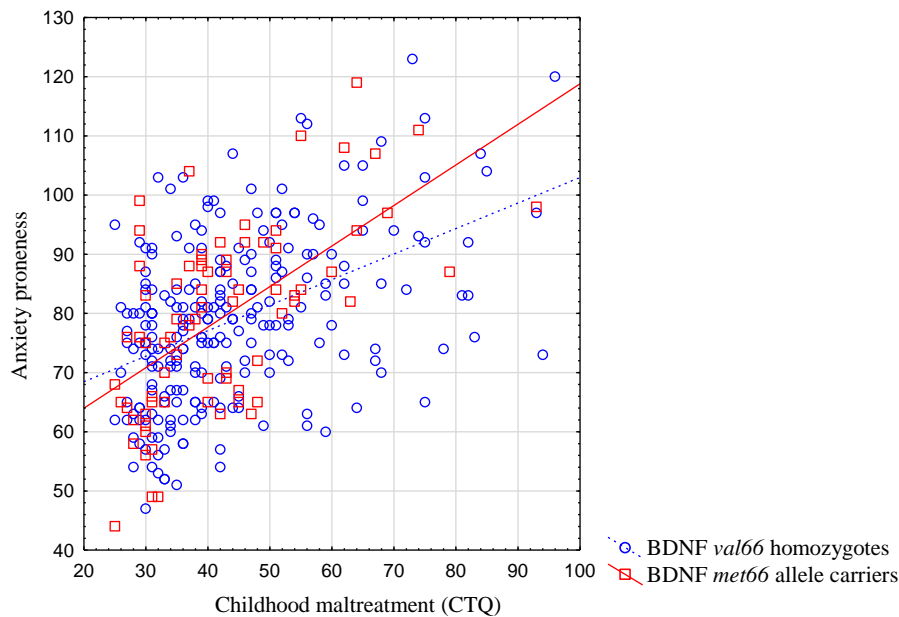


Figure 1. Association between childhood maltreatment and anxiety proneness level stratified by BDNF genotype. The figure indicates the correlation between childhood maltreatment scores and anxiety proneness scores in *Met66* allele carriers, reflected in the solid red line ($r=0.60$, $p<0.01$) and *Val66* homozygotes, reflected in the dashed blue line ($r=0.45$, $p<0.01$).

Discussion

Anxiety-related temperamental traits, such as AS, TA, and neuroticism, are said to be interactively impacted by genetic and environmental factors, such as CM and early life stress. This study investigated whether the BDNF *Val66Met* polymorphism interacted with CM to increase susceptibility to AP in a sample of mixed race adolescents. To our knowledge, this is the first study to assess the role of BDNF *Val66Met* in AP in a South African mixed race sample of adolescents.

Our results revealed a significant main effect of CM on AP, however no significant main effect of BDNF genotype on AP was determined. These findings suggest that the BDNF *Val66Met* polymorphism is not a direct contributing factor to AP susceptibility, as is CM. This finding is in line with studies that have found no significant direct association between BDNF *Val66Met* polymorphism and personality traits such as neuroticism, harm avoidance; and anxiety disorders or mood disorders, including OCD, panic disorder, PTSD, and depression (Arias et al., 2012; Chen et al., 2013; Frustaci et al., 2008; Hong et al., 2012; Minelli et al., 2011; Surtees

et al., 2007; Terracciano et al., 2010), despite some studies reporting such associations (Frustaci et al., 2008; Lang et al., 2005; Min et al., 2013; Montag et al., 2010; Sen et al., 2003; Terracciano et al., 2010). Firstly, the grouping of *Met66* allele carriers (i.e. *Met66Met* and *Val66Met* genotypes), as is frequently carried out in studies in which the rate of the *Met66Met* genotype is relatively low, such as in Caucasian samples (Gatt et al., 2009; Lehto, Maestu, Kiive, Veidebaum, & Harro, 2016; Nedic et al., 2013; Pivac et al., 2009), may introduce a bias in which a main effect of genotype is not detected due to the exclusion of the *Met66Met* genotype in analyses (Notaras et al., 2015). Secondly, the *Val66Met* and *Met66Met* genotypes, respectively, may have dissimilar effects (Hong et al., 2012). Nevertheless, the main effect of CM on AP determined in this study of adolescents provides support for the positive association between stressful life events and AP (McLaughlin & Hatzenbuehler, 2009), a well-established cognitive risk factor for the development of psychopathology, including anxiety disorders and associated symptoms in youth (Hishinuma et al., 2001; McLaughlin et al., 2007; Muris et al., 2001). Furthermore, our finding adds to the well-established literature demonstrating the adverse acute and long-term effects of CM or trauma on mental health and cognition in youth and adults (De Bellis, Woolley, & Hooper, 2013; Greger, Myhre, Lydersen, & Jozefiak, 2015; Irigaray et al., 2013; Taillieu, Brownridge, Sareen, & Afifi, 2016; Teicher, Ohashi, Lowen, Polcari, & Fitzmaurice, 2015).

Our results demonstrate a trend to a significant BDNF genotype x CM interactive effect on AP levels, suggesting that there may be a BDNF genotype x childhood adversity effect on AP. Specifically we found that adolescent *Met66* allele carriers, who reported high levels of CM, tended to have increased levels of AP. This trend is consistent with studies that have found that the low-functioning BDNF *Met66* allele and CM/childhood trauma or early life adversity or stress, interact to predict increased susceptibility for psychopathology, including anxiety-related temperamental traits, such as neuroticism (Gatt et al., 2009) and guilt-proneness (Szentágotai-Tótar et al., 2015); anxiety symptoms (Gatt et al., 2009); and mood disorders and associated symptoms (Aguilera et al., 2009; Carver et al., 2011; Gutiérrez et al., 2015). In addition, our results tend to support the interaction of the *Met66* allele and greater early adversity on reduced hippocampal and amygdala volumes and working memory deficits (Gatt et al., 2009). That said, our findings are not in agreement with G x E studies that have found an interactive effect of the higher functioning *Val66* allele and environmental exposures (i.e. adversity, negative stressors, recent life events) on psychopathology, such as increased levels of neuroticism, harm avoidance, and depression (Chen et al., 2013; Kim et al., 2009; Lehto et

al., 2016). Apart from the possible confounding effects of age and gender, discrepant results across studies may in part be due to population-driven differences in BDNF *Val66Met* frequencies, given that the *Met66* allele has been consistently been found to be more common in Asian populations than in Caucasian populations (Chen et al., 2013; Petryshen et al., 2009). A further confounding factor may include phenotype heterogeneity and methodological (assessment) differences (Hong et al., 2012).

Limitations

A number of study limitations should be taken into account in interpreting the current findings. First, due to the cross-sectional nature of this study, inferences about causality cannot be made. Second, our sample size of $N=308$ is relatively small given the estimated sample sizes required in candidate gene studies in which functional polymorphisms are assessed and in which minor effects are expected (Duncan & Keller, 2011). Third, use of the CTQ, a retrospective, self-report measure of CM, may have introduced moderate recall bias which may have resulted in the over- or under-reporting of maltreatment frequency. Fourth, we explored one polymorphism within the BDNF gene. Finally, we did not correct for gene-environment correlation (rGEs) or population stratification. The South African mixed race population is characterized by high levels of admixture (Tishkoff et al., 2009) and ancestral diversity (i.e. Khoesan, European, and Asian ethnicity) (Hemmings et al., 2016; Wright, Niehaus, Koen, Drögemöller, & Warnich, 2011), suggestive of genetic heterogeneity, which may have influenced our results. Findings of this exploratory study are therefore preliminary.

Conclusions

Our findings add to the literature on etiological processes that may underlie the development of anxiety-related traits, symptoms and disorder in adolescents. More specifically, our findings shed light on the role of the BDNF *Val66Met* polymorphism in the development of anxiety-related traits in mixed race adolescents in the context of childhood adversity. Furthermore, these results extend findings of the role of BDNF and CM on AP. Previous studies have focused on convenience samples of college students, or adults, and predominantly on the effects of the *5-HTTLPR* polymorphism (Hemmings et al., 2016; Kim et al., 2009; Klauke et al., 2011; Laucht et al., 2009; Stein et al., 2008). Our results suggest that the influence of CM on adolescent AP levels was moderated by the BDNF *Val66Met* polymorphism, with the *Met66*

allele tending to be associated with greater vulnerability to AP when levels of CM were high. Our findings highlight the importance of assessing gene-environment interactions in the assessment of genetic effects on anxiety-related phenotypes associated with anxiety disorders. Recommendations for future research include replication in larger samples of mixed race participants in which population stratification is corrected for and in which the *Met66Met* genotype is better represented (Notaras et al., 2015). Furthermore, variation across the BDNF gene would be useful to consider (Mandelman & Grigorenko, 2012). Additionally, the effect of other genetic variants, in conjunction with the BDNF *Val66Met* polymorphism, should be explored given findings of an epistatic effect between BDNF and the serotonin transporter genes (Martinowich & Lu, 2008; Pezawas et al., 2008). Further support for the aforementioned is reflected in findings of gene x gene and gene x gene x environment interactions which are indicative of significant interaction effects of the BDNF *Val66Met* polymorphism and the serotonin transporter gene (*SLC6A4*) on anxiety-related traits (e.g. neuroticism and harm avoidance) (Arias et al., 2012; Terracciano et al., 2010), and depressive symptoms and disorder (Gutiérrez et al., 2015; Kaufman et al., 2006). Finally, individual abuse and neglect types, as well as other environmental influences [e.g. parenting rearing practices (Ibarra et al., 2014) and general self-efficacy (Schiele et al., 2016)] on AP, should be explored. Investigation of the aforementioned would provide a clearer understanding of the genetic and environmental impacts on AP in mixed race, adolescent samples.

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Disclosure of interest

The authors report no conflicts of interest.

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CHAPTER 7

OVERVIEW OF FINDINGS

7.1 Introduction

The overall aim of this study was to investigate the effects of low and high levels of childhood maltreatment (CM) and anxiety proneness (AP) on neuropsychological performance and emotion processing in a representative sample of adolescents recruited from public secondary schools in Cape Town, South Africa. In addition, the study aimed to assess the interactive effect of the BDNF *Val66Met* polymorphism and CM on susceptibility to AP in a subsample of mixed race adolescents. Furthermore, the role that gene-environment (GxE) interactions (i.e. selected serotonin transporter variants and childhood maltreatment) play in modulating levels of anxiety sensitivity (AS) in Black and mixed race adolescents, was assessed (Hemmings et al., 2016).

The first tier of the study allowed for the successful screening and collection of salivary DNA from 1149 secondary school students from 29 public schools in Cape Town. Four groups of adolescents, comprising 111 participants in total, grouped according to levels of tier 1 self-reported CM and AP, and matched as closely as possible on tier 1 age, ethnicity, gender, and tier 1 educational status, were subsequently included in the second tier of the study and underwent a neuropsychological and neuroimaging assessment, amongst others.

To the best of our knowledge, this is the first study to assess neuropsychological performance and emotion processing in a non-clinical South African sample of adolescents with varying levels of both CM and AP. Similarly, to our knowledge, this was the first study to assess the moderating role of BDNF *Val66Met* in the relationship between CM and AP in a South African mixed race sample of adolescents; and the first study to investigate the role of 5' and 3' variants in the serotonin transporter gene in AS in Black and mixed race South African adolescents (Hemmings et al., 2016). This study makes an important contribution in documenting the potential influence of varying levels of CM and AP on neuropsychological performance and emotion processing in non-clinical adolescents from a lower-middle income, developing country setting. In addition, this study contributes to our understanding of the role of the BDNF *Val66Met* gene and serotonin transporter variants in the development of anxiety-related traits in non-Caucasian adolescents, in the context of CM.

A comprehensive discussion of study findings is presented in each discussion section of chapters 4, 5, and 6. In terms of the assessment of the role of serotonin transporter variants in AS, a comprehensive discussion of findings is presented in the attached published manuscript (i.e. Appendix A1; Hemmings et al., 2016).

7.2 Overview of key study findings

7.2.1 The effects of childhood maltreatment and anxiety proneness on neuropsychological performance in non-clinical older adolescents

Evidence exists for neuropsychological performance differences in youth with histories of CM, however, studies have largely compared youths according to the presence or absence of a history of CM (e.g. Kirke-Smith et al. 2014) and the presence or absence of a current clinical disorder (e.g. De Bellis et al. 2013). Relatively few studies have assessed neuropsychological functioning in non-clinical adolescents with varying levels of CM (e.g. Spann et al. 2012). Similarly, despite there being some evidence for neuropsychological performance differences associated with increased levels of AP, studies in non-clinical adolescents are few (e.g. MacLeod and Donnellan 1993; Owens et al. 2008). We explored the predictive ability of CM and AP, as well as the interaction of these, on neuropsychological performance, including IQ, visual and verbal memory and learning, executive functioning skills (e.g. cognitive flexibility, verbal fluency, and verbal working memory), processing speed, and visuo-spatial skills, in our sample of adolescents (n=104). Controlling for important confounds, including socio-economic status, self-reported depression, and ethnicity, we determined the following:

- (1) Lower neuropsychological test scores in terms of (1) executive functioning skills, including, cognitive flexibility and verbal fluency; (2) processing speed; and (3) IQ; were associated with the interaction between CM and AP, with poorer performance in these neuropsychological domains evident in those adolescents reporting lower levels of AP and higher levels of CM, relative to those adolescents reporting lower levels of AP and CM;
- (2) high levels of AP, regardless of level of CM, were associated with lower scores in cognitive flexibility, verbal fluency, processing speed, and IQ;
- (3) CM and AP uniquely predicted verbal working memory performance; and
- (4) neither CM nor AP (nor the interactive effect of CM and AP) were predictive of verbal and visual memory and learning performance, or visuo-spatial abilities in our

sample.

These findings provide evidence for the unique and combined effects of CM and AP on a number of important neuropsychological domains in our non-clinical sample of adolescents.

7.2.2 Emotion processing in a non-clinical sample of older adolescents with high and low levels of both anxiety proneness and childhood maltreatment

Numerous neuroimaging studies have determined that youth with CM histories demonstrate deficits in emotion processing, with such deficits reflected in hyperactivity of the amygdala, hippocampus and insula in response to processing salient stimuli (Maheu et al., 2010; McCrory et al., 2011; McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015; Tottenham et al., 2011). Similar findings have been noted in AP youth (Etkin et al., 2004; Stein, Simmons, Feinstein, & Paulus, 2007), however, studies have been few and most studies in both CM and AP have commonly employed tasks that depict facial expressions of emotion to assess affective processing. We explored the unique and combined effects of CM and AP on emotion processing in bilateral amygdala, hippocampus and insula in our sample of adolescents (n=78). In addition, we hypothesized that adolescents with high levels of both CM and AP would demonstrate significantly more pronounced neural deficits relative to adolescents with comparable levels of CM who have low levels of AP. Key findings from this analysis indicated that:

- (1) neither CM nor AP had any significant main or combined effects on matching accuracy or reaction times;
- (2) no significant differences in matching accuracy or reaction times were evident across the four groups;
- (3) neither CM nor AP had any significant main or combined effects on neural responses to negative or positive images, relative to neutral images, in the amygdala, hippocampus or insula;
- (4) no significant group differences in terms of neural responses in bilateral amygdala, hippocampus or insula were observed;
- (5) a trend for greater activation in response to negative and positive images in the right amygdala was evident in anxiety prone adolescents relative to those adolescents with low AP levels; and
- (6) CM did not have differential effects on emotion processing outcomes

These findings suggest that comparable performance, in terms of both task dependent behaviour and neural responses to processing salient content, was evident in our adolescent sample, regardless of levels of CM or AP. Adolescents with increased levels of both CM and AP performed comparably to those adolescents with high levels of CM and low levels of AP.

7.2.3 Gene-by-environment interaction of BDNF *Val66Met* polymorphism and childhood maltreatment on anxiety proneness in a mixed race adolescent sample

Both CM and AP have consistently been implicated as risk factors for psychopathology, including anxiety disorders (Collishaw et al. 2007; McLaughlin et al. 2007; Kessler, McLaughlin, et al. 2010; McLaughlin et al. 2012). In addition, evidence exists for a moderating role of BDNF *Val66Met* in the relationship between life stress, including abuse and neglect, and subsequent risk for psychopathology in adolescents and young adults (Carver et al. 2011; Chen et al. 2013). We explored the interactive effect of the BDNF *Val66Met* polymorphism and CM to increase susceptibility to AP in a sub-sample of mixed race adolescents (n=308) from the first tier of the study. Key findings from this analysis are as follows:

- (1) genotype frequencies in our mixed race sample were generally consistent with those determined in Caucasian samples;
- (2) CM had a significant main effect on AP, but BDNF genotype did not; and
- (3) there was a trend toward statistical significance in terms of an interaction effect of the BDNF *Met66* allele (relative to *Val66* homozygotes) and CM on AP.

These findings suggest that the BDNF *Val66Met* polymorphism is not a direct contributing factor to AP susceptibility, as is CM. Furthermore, a trend to a *BDNF* genotype by childhood adversity effect on AP was evident. This trend is in line with those studies that have found that the low-functioning BDNF *Met66* allele and childhood trauma or childhood adversity or stress, interact to predict increased susceptibility for psychopathology, including anxiety-related temperamental traits (Gatt et al., 2009) and anxiety symptoms (Gatt et al., 2009).

7.2.4 Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents (Hemmings et al., 2016)

The serotonin transporter gene (gene, *SLC6A4*; variant, 5-HTTLPR) has been extensively investigated in the context of childhood anxiety (Murray, Creswell, & Cooper, 2009). The short

(*S*) allele of the 5-HTTLPR polymorphism, relative to the long (*L*) allele, has been found to be associated with a predisposition to anxiety, such as increased levels of neuroticism, harm avoidance, and trait anxiety (Gonda et al., 2009; Katsuragi et al., 1999; Schinka, Busch, & Robichaux-Keene, 2004). Furthermore, the 5-HTTLPR genotype has previously been found to interact with CM to increase susceptibility to AS (Klauke et al., 2011; Stein et al., 2008). We investigated the role that G x E interactions, namely, CM and selected *SLC6A4* variants, play in modulating AS levels in Black and mixed race adolescents (Hemmings et al., 2016). Key findings from this analysis were as follows:

- (1) a significant association between 5-HTTLPR and AS was observed in male mixed race adolescents, but not in Black or female mixed race adolescents. This association indicated that male mixed race *S*-homozygotes had significantly higher AS scores than male mixed race *LL* or *LS* genotypes;
- (2) reduced AS was associated with the 5-HTTLPR-rs25531 *LG* haplotype among Black adolescents; and
- (3) the rs1042173 *CC*-genotype was found to be protective against increased AS levels in Black adolescents who had experienced increased CM.

These findings suggest that the 5' and 3' variants in the serotonin transporter gene are able to both independently and differentially affect AS levels in non-Caucasian adolescents. In addition, findings shed light on the role that *SLC6A4* plays in anxiety-related traits and disorders (Hemmings et al., 2016).

7.3 Contribution to knowledge gaps

- (1) The majority of studies that have assessed either clinical, neuropsychological functioning, or emotion processing in youths with high levels of anxiety-related temperamental traits and histories of CM, have been conducted in high resource, first and second world countries, or developed countries, and among predominantly Caucasian samples. South Africa is a developing, low-middle income, low resource country, and many children and adolescents are exposed to high levels of poverty, violence, and trauma, all established risk factors for poor child and adolescent mental health (Patel, Flisher, Nikapota, & Malhotra, 2008). In addition, mental health resources in South Africa are considerably lower than in higher income countries, and therefore, vulnerable populations, such as children and adolescents, may not be

provided with appropriate evidence-based mental health care (Bruckner et al., 2011) and may be at increased risk for the development and maintenance of psychopathology. To date, no studies have assessed both neuropsychological functioning and emotion processing as a function of both AP and history of CM in predominantly non-Caucasian, non-clinical adolescents, within a developing country context such as South Africa. The present study is the first in South Africa to extensively assess a broad range of neuropsychological domains, as well as assess and compare functional activation in brain structures associated with emotion processing, in primarily Black and mixed race, non-clinical adolescents with both high and low levels of CM and AP.

- (2) This study provides evidence for multiple differences in a number of important neuropsychological domains as a result of both the combined and individual effects of CM and AP in predominantly non-Caucasian, non-clinical adolescents.
- (3) Most neuroimaging studies in youth that have assessed emotion processing have employed tasks that depict facial expressions of emotion to elicit functional responses, and most of these studies have been conducted in samples of Caucasian youths. It has been suggested that tasks employing facial expressions of emotion involve emotion recognition, whereas tasks that entail observing IAPS images are thought to involve the direct experience of emotion (Britton, Taylor, Sudheimer, & Liberzon, 2006). In comparison with studies that have employed facial expressions of emotion to assess emotion processing in youth, few studies have used images from the IAPS. This is the first study to use pleasant and unpleasant images, relative to neutral images, to explore the combined and individual effects of CM and AP on emotion processing in non-clinical, predominantly non-Caucasian adolescents.
- (4) This study provides evidence for comparable performance in both task-dependent behaviour and brain functional responses during the processing of pleasant and unpleasant images, where neither the severity of CM nor the severity of AP significantly affected these domains.
- (5) This study provides preliminary evidence for a likely effect of AP in response to pleasant and unpleasant images in the right amygdala in non-clinical adolescents. This finding warrants further investigation in larger sample sizes so as to provide further clarity on the relationship between AP and right amygdala reactivity to salient images.

- (6) The current study is the first study, to our knowledge, to investigate the interactive effects of the BDNF *Val66Met* polymorphism and CM in increasing susceptibility to AP in a sample of mixed race adolescents. This study provides preliminary evidence for the moderating role of BDNF *Val66Met* in the association between CM and increased risk of anxiety-related phenotypes in our mixed race sample. Further investigation in larger samples of mixed race adolescents is warranted so as to confirm the role of the BDNF *Val66Met* polymorphism in the relationship between CM and AP.
- (7) The current study is the first study, to our knowledge, to investigate the role of 5' and 3' variants in *SLC6A4* in AS in a South African Black and mixed race adolescent sample. Findings from this study suggest that the 5' and 3' ends of the gene may independently and differentially affect levels of AS within our ethnically diverse sample of adolescents.

7.4 Limitations

The findings of this study must be viewed within the context of the limitations of the study.

- (1) Given the cross-sectional nature of the study, inferences about causality cannot be made (Mann, 2003; Sedgwick, 2014). Longitudinal studies are required to investigate the potential trends in outcomes over time (Sedgwick, 2014).
- (2) Almost three quarters of the sample was female. Furthermore, over three quarters of the sample self-identified as Black, and over one fifth as mixed race. Our findings may therefore not generalize to male adolescents or to ethnic groups other than Black and mixed race.
- (3) This study relied on self-report measures to determine participants' levels of CM and AP, amongst others. The use of self-report measures may have resulted in the over- or under-reporting of symptoms which may have influenced our findings (Lanyon & Wershba, 2013; Mathiowetz & Dipko, 2000; McCart et al., 2005).
- (4) The Childhood Trauma Questionnaire (CTQ-SF; Bernstein et al., 2003) which was used in this study is a retrospective measure of CM and may therefore have introduced moderate recall bias. That said, participants screened in the first tier of the study consisted predominantly of adolescent participants with the second tier of the study

consisting solely of adolescents. Given that we enquired about maltreatment prior to the age of 12 years, recall bias was likely minimal.

- (5) The vast majority of self-report instruments, as well as neuropsychological instruments utilized in this study, have not been validated in a South African adolescent sample. This limitation highlights the need for standardized measures (i.e. both neuropsychiatric and neuropsychological) to adequately identify adolescents at risk of mental health problems (de Vries, Davids, Mathews, & Aarø, 2017).
- (6) The structured diagnostic interview and the neuropsychological evaluation were conducted in either English or Afrikaans and not in the Xhosa language. As cultural factors impact the understanding of language, and the assessment of neuropsychological performance is dependent on both language ability and language recognition, measurement bias may have been introduced and may have influenced the neuropsychological assessments of Xhosa-speaking participants, resulting in an overestimation of low performance (Olmedo, Berg, Mejnartowicz, & Walke, 2012).
- (7) The IAPS task has not been validated in a South African adolescent population. Our findings must therefore be considered preliminary given the exploratory nature of this study.
- (8) In terms of employing general linear modelling to assess differences across our four groups of interest, the relatively small sample sizes may have influenced the statistical power to detect both CM-related impairments and dispositional anxiety-related impairments in neuropsychological and neuroimaging outcomes (Maxwell, 2004).
- (9) Furthermore, multiple comparisons may have increased the risk of Type I errors (Cramer et al., 2016). The findings from this study must therefore be considered preliminary given the exploratory nature of this study.
- (10) In our analysis of the gene-by-environment effect of BDNF *Val66Met* polymorphism and CM on susceptibility to AP, we did not correct for gene-environment correlation or population stratification. The South African mixed race population is characterized by high levels of admixture and ancestral diversity (Tishkoff et al., 2009; Wright, Niehaus, Koen, Drögemöller, & Warnich, 2011), suggestive of genetic heterogeneity, which may have influenced our results.
- (11) In our analysis of the role that serotonin transporter variants play in AS in South African Black and mixed race adolescents, we did not correct for gene-environment correlation or population stratification in either the Black or mixed-race groups. The Black, Xhosa-speaking population is less likely to present with genetic and phenotypic

heterogeneity given that this population is characterized by ethnic and cultural isolation (Niehaus et al., 2005). On the other hand, as indicated above, the South African mixed race population is characterized by high levels of admixture and ancestral diversity (Tishkoff et al., 2009; Wright et al., 2011), suggestive of genetic heterogeneity, which could confound results in this study group.

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CHAPTER 8

CONCLUSION AND RECOMMENDATIONS FOR FUTURE RESEARCH

8.1 Conclusion

In conclusion, this study demonstrated that older adolescents with higher levels of childhood maltreatment (CM) histories and higher levels of anxiety proneness (AP) are at risk for poorer neuropsychological performance in a number of important neuropsychological domains. In particular, increased levels of CM and AP have independent effects on working memory performance, such that increased levels of CM and AP are uniquely associated with poorer working memory outcomes. Findings also provided evidence for the combined effects of CM and AP on a range of outcomes (i.e. cognitive flexibility, verbal fluency, processing speed, and IQ), with findings suggesting that the influence of CM on the aforementioned domains is dependent on the level of AP (i.e. adolescents with lower levels of AP are affected by higher levels of CM, however, CM level does not seem to impact these domains when AP levels are high). These findings are in keeping with those studies conducted predominantly in developed countries among Caucasian youths that have demonstrated the adverse impact of CM and AP on neuropsychological functioning (De Bellis, Woolley, & Hooper, 2013; De Bellis, Hooper, Spratt, & Woolley, 2009; Kavanaugh & Holler, 2014a, 2014b; Masson, Bussi  res, East-Richard, R-Mercier, & Cellard, 2015; Mothes et al., 2015). Our results with regard to the significant interactive effect of CM and AP on certain neuropsychological domains extend previous findings of the impact of both CM and AP on neuropsychological performance in non-clinical adolescents.

Numerous studies have demonstrated pronounced neuropsychological differences in youths or young adults with anxiety disorders (Castaneda, Tuulio-Henriksson, Marttunen, Suvisaari, & L  nnqvist, 2008; Toren et al., 2000), youths with documented histories of CM (Vasilevski & Tucker, 2016), and youths with both maltreatment histories and clinical disorder, such as posttraumatic stress disorder, amongst others (De Bellis et al., 2013; De Bellis et al., 2009; Kavanaugh & Holler, 2014b). Our results extend previous findings and demonstrate that certain neuropsychological domains are interactively impacted by CM and AP, and neuropsychological difficulties are not restricted to adolescents with clinical disorder(s) or to

adolescents with documented histories of abuse and neglect, but are also applicable to youth with sub-threshold forms of anxiety and youth with elevated levels of self-reported CM.

With regard to our fMRI findings associated with emotion processing, no evidence was found for any main or combined effects of CM or AP on emotion processing outcomes, either in terms of task-dependent behaviour or in neural responses to salient images, relative to neutral images from the IAPS (Lang, Bradley, & Cuthbert, 1997). Our results therefore suggest that neither CM levels nor AP level significantly impacted emotion processing in our non-clinical sample of adolescents. The trend for greater activation in the right amygdala to negative and positive images, relative to neutral images, in adolescents with increased AP levels, suggests that right amygdala hyperactivity may be a neural correlate of AP in non-clinical adolescents, however, further investigation in larger samples of adolescents is warranted. Findings of increased amygdala reactivity to both pleasant and unpleasant stimuli (i.e. facial expressions and images) is in keeping with previous findings in non-clinical individuals (Fusar-Poli et al., 2009; Garavan, Pendergrass, Ross, Stein, & Risinger, 2001) and in AP individuals (Cunningham, Arbuckle, Jahn, Mowrer, & Abduljalil, 2011; Stein et al., 2007). Given that substantial differences in amygdala and prefrontal cortex activation is evident during adolescence (Casey, Jones, & Somerville, 2011), and that great variation in neural responsivity (e.g. in the amygdala) to emotional stimuli has been noted in healthy adolescents, over time (Van Den Bulk et al., 2013), such variation may have implications for treatment as pre-treatment amygdala responsivity to negative and neutral stimuli has been reported to be associated with symptom reduction during trauma-focused cognitive-behavioural therapy in physically and sexually abused adolescents (Cisler et al., 2015).

This study provides preliminary support for the moderating role of BDNF *Val66Met* in the association between CM and increased vulnerability to AP in mixed race adolescents. Adolescents who were *Met66* allele carriers tended to be more vulnerable to increased AP when they also had higher levels of CM. This gene-by-environment interaction effect on AP trended towards significance, and therefore, replication in larger samples of mixed race adolescents is required to clarify these relationships. Lastly, our results suggest that selected *SLC6A4* variants play a role in anxiety sensitivity (AS) in non-Caucasian adolescents. In male mixed race adolescents (but not in Black or female mixed race adolescents), *S*-homozygotes had significantly higher AS scores than male mixed race *LL* or *LS* genotype carriers. In Black adolescents (but not in mixed race adolescents), the 5-HTTLPR-rs25531 *LG* haplotype, but not

the *LA* haplotype, was associated with reduced AS. Furthermore, in Black adolescents (but not mixed race adolescents), the rs1042173 CC-genotype protected against increased levels of AS in those adolescents that also reported high levels of CM. These findings highlight the possibility that the 5' and 3' ends of the gene independently and differentially affect levels of AS within Black and mixed race adolescents.

8.2 Directions for future practice and research

8.2.1 Recommendations for practice

The evidence for significant unique and combined effects of CM and AP on neuropsychological performance in our non-clinical sample of older adolescents highlights the need and importance of screening adolescents for both histories of CM and anxiety-related temperamental traits, such as AS and trait anxiety (TA), regardless of their clinical status. Such screening will aid in the early identification of youths who may be in need of support and subsequent treatment.

Our findings have important clinical implications given that neuropsychological abilities can significantly impact an individual's ability to function adequately in both social and academic/work contexts (Castaneda et al., 2008). Furthermore, lower neuropsychological performance in children and adolescents has been found to be associated with the development of problem behaviour (e.g. conduct problems), risky behaviour (e.g. substance use) (Giancola & Tarter, 1999; Hill, 2002), an increased risk for poor academic performance and scholastic achievement (e.g. attainment in mathematics, science, English, and reading performance) (Best, Miller, & Naglieri, 2011; Laidra, Pullmann, & Allik, 2007; Rajchert, Zulfak, & Smulczyk, 2014; Sikora, Haley, Edwards, & Butler, 2002; St Clair-Thompson & Gathercole, 2006), and attentional and behavioural problems at school (Aronen, Vuontela, Steenari, Salmi, & Carlson, 2005).

Our findings of the significant impact of CM and AP on various outcomes assessed, underscores the importance for early intervention, with a particular focus on the reduction or prevention of CM, the reduction in levels of AP, the improvement of neuropsychological skills, and the improvement of psychological wellbeing in youth. Research to date has provided

evidence for a number of successful interventions which, to some degree, have addressed these needs.

In terms of interventions aimed at preventing or reducing CM, some individual interventions that commonly focus on both child and family factors associated with CM, have been found to be effective. Such interventions, which include, for example, routine perinatal care together with antenatal and postnatal nurse home visits to vulnerable families with young children, have reported significantly improved mother-infant interactions (Barlow et al., 2007), and fewer reports of CM (Eckenrode et al., 2000). In addition, parenting and family support interventions which promote, for example, the improvement of parenting skills, safe and nurturing environments for children, and social, behavioural and emotional competencies of children, have shown to be effective (Nowak & Heinrichs, 2008). Interventions aimed at providing support to families that face family or parenting problems have reported long-term improvements in parenting skills and reduced behaviour problems in children (Hermanns, Asscher, Zijlstra, Hoffenaar, & Deković, 2013). In terms of community-based interventions, there is a lack of evidence for the effectiveness of such interventions, due in part to difficulties associated with evaluating outcomes and that effects of these interventions may vary by context (van Dijken, Stams, & de Winter, 2016). Furthermore, there is strong evidence for both individual and group cognitive-behavioural therapy in reducing psychological symptoms, such as posttraumatic stress symptoms, associated with trauma exposure in children and adolescents (Wethington et al., 2008). Trauma-focused cognitive-behavioural therapy for adolescents and parents has also been found to be an effective treatment approach for traumatized youth, including those with abuse histories, with improvements noted in a range of trauma-related psychological and behavioural symptoms (Cohen & Mannarino, 2008).

Cognitive-behavioural interventions have been found to be effective in reducing AS in clinical and at-risk samples of adults (Smits, Berry, Tart, & Powers, 2008). Similarly, a telephone-delivered cognitive behavioural therapy intervention in treatment seeking adults was found to be effective in reducing AS, as well as panic, posttraumatic stress, and social phobia symptoms, in the long term (Olthuis, Watt, Mackinnon, & Stewart, 2014). Furthermore, support for the effectiveness of a computer-assisted AS intervention (i.e. which involved both psychoeducation about stress and anxiety-related symptoms, and brief interoceptive exposure) in reducing levels of AS, anxiety, depression and worry, and increasing levels of distress tolerance in college students, has been determined (Norr, Allan, Macatee, Keough, & Schmidt,

2014). There is also evidence for the effectiveness of a single session of motivational enhancement therapy in reducing levels of AS in college students, with the level of reduction in AS being similar to reductions noted in other cognitive behavioural techniques (Korte & Schmidt, 2013).

The effectiveness of a school-based social competence intervention for adolescents has recently been demonstrated, with findings of improved social responsiveness, social cognition, social communication and motivation in adolescent students, being noted (Stichter, Herzog, Owens, & Malugen, 2016). Moreover, improvements in students' executive functioning skills, both at school (e.g. improvement in working memory and the ability to plan ahead) and at home (e.g. improvements in ability to shift between task and better control of emotions) were reported (Stichter et al., 2016). In addition, there is tentative evidence for the effectiveness of online mental health promotion and prevention interventions aimed at youth in reducing symptoms of anxiety and depression, avoidant coping, psychological distress; and improving psychological wellbeing and support-seeking coping strategies (Clarke, Kuosmanen, & Barry, 2014).

Most studies discussed above have, however, been implemented in high resource, developed, high-income countries. In comparison, South Africa is a low resource, developing, low- to middle-income country (LMIC), characterized by high levels of unemployment, income inequality, poverty, violence exposure, and HIV/AIDS (Makoe, Roberts, & Ward, 2012; Martin, 2010). These factors negatively impact the well-being and mental health of children and adolescents and contribute to the challenges of implementing effective and affordable prevention interventions (Makoe et al., 2012; Patel, Flisher, Nikapota, & Malhotra, 2008). That said, a number of important government and non-government funded programs and services exist for vulnerable children and adolescents, some of which are solely dedicated to the prevention of CM (Makoe et al., 2012; Martin, 2010) and the reduction of child abuse (Cluver et al., 2016). Furthermore, in the last decade, considerable progress has been made in the provision of mental health care services in South Africa, such as the provision of mental health services at the community level (Jack-Ide, Uys, & Middleton, 2012), as well as the introduction of the Integrated School Health Programme (ISHP) in 2012. The ISHP aims to, amongst others, improve the general health of school-going children (including mental health and address abuse, bullying, and violence) and aims to address health barriers to learning (National Department of Health and National Department of Basic Education, 2012). Despite this aforementioned progress, a number of significant challenges still remain (Petersen & Lund,

2011). Currently substantial efforts are being made to improve and strengthen mental health services in low- and middle-income countries, such as South Africa (Semrau et al., 2015).

There is strong evidence to support the implementation of mental health interventions (i.e. spanning promotion, prevention, and treatment) in schools in low- and middle-income countries (LMICs), using a whole-school approach (Fazel, Patel, Thomas, & Tol, 2014). In particular, the delivery of mental health promotion interventions in schools (e.g. those that improve resilience, coping skills and life skills) in LMICs is practical, feasible, and scalable, and increased effectiveness of such interventions is associated with interventions that are more structured and implemented over longer periods of time. In terms of mental health prevention and treatment interventions in schools in LMICs, the effectiveness of such interventions appears more complex, given that approximately half of the studies assessed in a systematic review had positive findings (Fazel et al., 2014). A number of school-based mental health interventions (i.e. promotion and disorder prevention) in LMICs have trained teachers and lay counsellors to deliver interventions, with mixed results being reported. For example, some studies have noted the most positive effects on posttraumatic stress disorder symptoms, with some success determined for depression symptoms, behaviour and conduct (Fazel et al., 2014). Teachers and school counsellors can be utilized to deliver mental health interventions in schools, however, the implementation of such interventions can be hampered by time constraints, heavy workloads, and competing priorities commonly faced by teachers in LMIC schools (Hill et al., 2015; Fazel et al., 2014). A role for lay community members in the delivery of mental health interventions in LMIC schools has also been determined (Rajaraman et al., 2012; van Ginneken et al., 2013). In addition, there is evidence to suggest that peer education (e.g. how to find assistance and support for experienced problems, effective decision-making skills, sexual risk behaviour, and substance abuse) is a key health promotion strategy in LMIC schools, including South African schools, with indirect positive effects noticed in terms of improved communication skills, school performance, and improved ability to cope with traumatic experiences, including abuse and violence exposure (Swartz & Moolman, 2015).

8.2.2 Recommendations for future research

Our sample consisted primarily of female adolescents and the majority of the sample self-identified as Black, followed by mixed race. It will be important therefore for future studies to replicate the study in adolescent samples in which ethnic groups are more evenly spread and

better represented. In addition, future studies should aim to include equal numbers of male and female adolescents to ensure that both genders are equally represented and that findings can adequately extend to male adolescents.

In terms of our assessment of the unique and combined effects of CM and AP on neuropsychological performance, it would be useful for future studies to examine the individual and combined effects of AP and CM types (i.e. abuse and neglect categories), as well as concurrent forms of CM, on neuropsychological outcomes, as these have been found to have differential effects on neuropsychological performance (Nolin & Ethier, 2007; Ogata, 2011). Furthermore, the effects of important moderator variables such as ‘age of onset of maltreatment’ and ‘duration of maltreatment’ should be assessed as these may play a role in neuropsychological outcomes (Delima & Vimpani, 2011; Jaffee & Maikovich-Fong, 2011; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006).

In terms of emotion processing, recommendations for future research include assessing the predictive potential of CM and AP, as well as the interactive effect of these, on emotion processing. Furthermore, replication in larger samples of adolescents in which both the main effects of maltreatment types, as well as the combined effect of maltreatment types and AP, on task performance are assessed, as emotion processing may have unique patterns of association with the various abuse and neglect categories (da Silva Ferreira, Crippa, & de Lima Osorio, 2014). Furthermore, variables such as ‘age of onset’, ‘maltreatment duration’ and ‘maltreatment severity’ will be useful to assess in future studies given that these have been found to impact limbic responses to emotional stimuli (da Silva Ferreira et al., 2014; McCrory et al., 2013). Lastly, functional connectivity analyses should be incorporated into future studies as such analyses will provide a better understanding of the regulatory responses associated with CM and AP (Greening & Mitchell, 2015; Herringa et al., 2016; Kim et al., 2011).

With reference to our preliminary finding that suggests that the BDNF *Val66Met* polymorphism has a moderating effect in the relationship between CM and AP, we recommend replication in larger samples of mixed race adolescents to confirm these relationships, as our finding of a gene-by-environment effect on AP was not significant at the 0.05 level, but trended towards significance ($p = 0.06$). Furthermore, it is recommended that future studies correct for population stratification; consider variation across the BDNF gene (Mandelman & Grigorenko, 2012); assess other genetic variants in conjunction with the BDNF *Val66Met* polymorphism

(Martinowich & Lu, 2008; Pezawas et al., 2008); and examine abuse and neglect types and other environmental influences [e.g. parental rearing practices (Ibarra et al., 2014)] on AP. With reference to our findings that suggest that certain *SLC6A4* variants play a role in AS in non-Caucasian adolescents, future studies are required to replicate the results of this study. As above, it is recommended that future studies correct for population stratification, and examine abuse and neglect types as well as other potential environmental influences on AP. The inclusion of these recommendations in future studies will allow for a clearer understanding of both genetic and environmental influences on AP.

Given that certain polymorphisms (e.g. the *S*-allele of 5-HTTLPR) have been shown to be associated with neuropsychological performance outcomes [e.g. poorer performance in working memory and visual memory tasks (Price et al., 2013; Zilles et al., 2012)] and deficits in emotion processing [such as greater attentional bias to fear stimuli, increased neural activity in frontal and limbic brain regions in response to negative stimuli (Hariri et al., 2002; Thomason et al., 2010; Walsh et al., 2012), and diminished prefrontal-down regulation of the amygdala (Jonassen & Landrø, 2014)], we aim to utilize our current data to assess the role of polymorphisms in specific candidate genes (e.g. 5-HTTLPR and *BDNF Val66Met*) in accounting for variance in neuropsychological and functional imaging outcomes in our sample. In addition, we aim to examine the interaction of genetic factors with neuropsychological processes and brain functional activity that may be important for mediating increased levels of anxiety in adolescents/young adults with increased anxiety-related temperamental traits and CM histories. Such an investigation may provide a clearer understanding of neurobiological mechanisms underlying the development of anxiety disorders.

A follow-up study to this study will be conducted in the near future and will include adolescents who participated in the second tier of this research. This follow-up study will aim to assess how psychological factors (e.g. posttraumatic stress symptoms, perceived stress and perceived social support), temperamental disposition (i.e. TA and AS), environmental influences (e.g. CM and life events), and neuropsychological performance outcomes (in verbal and visual memory, and executive functioning) are associated with the evolution and persistence of psychopathology in older adolescents and young adults. This follow-up study will allow for the better understanding of factors and influences that impact mental health in adolescents and young adults. It will also allow for the improved identification of young adults at risk of

developing anxiety disorders and who are in need of further evaluation, monitoring and treatment.

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APPENDIX A1:

Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents



ORIGINAL INVESTIGATION

Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents

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ABSTRACT

Objectives: Anxiety sensitivity (AS) has predictive potential for the development of anxiety disorders. We investigated the role that gene–environment ($G \times E$) interactions, focussing on childhood trauma (CT) and selected *SLC6A4* variants, play in modulating levels of AS in a South African adolescent population. **Methods:** All adolescents ($n = 951$) completed measures for AS and CT. Six *SLC6A4* polymorphisms were genotyped. $G \times E$ influences on AS levels were assessed using multiple linear regression models. Relevant confounders were included in all analyses. **Results:** Xhosa ($n = 634$) and Coloured ($n = 317$) participants were analysed independently of one another. The 5-HTTLPR-rs25531 L-G haplotype associated with reduced AS among Xhosa adolescents ($P = 0.010$). In addition, the rs1042173 CC-genotype protected against increased levels of AS in Xhosa participants who had experienced increased levels of CT ($P = 0.038$). Coloured males homozygous for the S-allele had significantly increased levels of AS compared to Coloured males with at least one L-allele ($P = 0.016$). **Conclusions:** This is the first study to be conducted on AS in adolescents from two ethnically diverse populations. Results indicate that the L-G haplotype confers protection against high AS levels in a Xhosa population. Furthermore, increased CT was found to protect against high levels of AS in Xhosa rs1042173 CC-carriers.

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Introduction

Anxiety sensitivity (AS) refers to the fear of anxiety-related bodily sensations, derived from the belief that these sensations may have harmful physical, psychological or social consequences (Reiss and McNally 2005). AS is not categorised as a clinical disorder, but has been reported to play an important role in the development of anxiety disorders, particularly panic disorder and posttraumatic stress disorder (PTSD), and has emerged as a significant risk factor in the development of anxiety disorders amongst children and adolescents (Reiss and McNally 2005; Schmidt et al. 2010). Some studies have indicated that the relationship between anxiety or anxiety symptoms and AS possesses a bidirectional dynamic, particularly in adolescents (Zavos et al. 2012a), whilst others have observed a unidirectional relationship, with AS serving as a risk factor for the development of anxiety disorders (Waszczuk et al. 2013).

AS has been suggested to have characteristics of both a trait (Reiss and Havercamp, 1996) and a learning

process (Schmidt et al. 2000), underscoring the importance of both genes and environment in its aetiology (Zavos et al. 2012b). Research has indicated that AS has heritabilities ranging between 37% in children (Eley et al. 2007) to 45–50% in adolescents and adults (Stein et al. 1999; Zavos et al. 2010). Heritability of AS has been found to be stronger amongst females. Jang et al. (1999) found that, in a sample of twins, AS was only heritable amongst females, with genetic factors accounting for approximately 45% of the variability in symptoms. Although genetic influences were observed to be stable for the most part, Zavos et al. (2012a, 2012b) also observed a period of “genetic flux” between the ages of 15 and 17 years, where new genetic influences emerged at certain stages of development. This finding points strongly towards the interactive effect that genes and environment may have on AS, leading to a number of recent publications investigating the interaction between candidate genetic variants and childhood

maltreatment on AS (Stein et al. 2008; Klauke et al. 2011; Zavos et al. 2012c; Baumann et al. 2013).

The serotonin transporter (solute carrier family 6 (neurotransmitter transporter), member 4 (*SLC6A4*)) is one of the most widely investigated genes in psychiatric disorders, given the key role that serotonin (5-HT) plays in their aetiology. The serotonin transporter gene (*SLC6A4*), located on chromosome 17q11.1–q12 (Heils et al. 1996), has been extensively investigated in the context of anxiety and depressive disorders, with a common insertion-deletion (indel) polymorphism being the most frequently investigated. This indel is situated in the promoter region of the gene, approximately 1 kilobase (kb) upstream of the transcription initiation site, in a region of the gene known as the serotonin transporter-linked polymorphic region (*5-HTTLPR*). The *5-HTTLPR* polymorphism comprises a short (S) allele and a long (L) allele, which differ in length by 44 bp. The polymorphism is reportedly functional, with the L-allele being more efficiently transcribed than the S-allele, resulting in more efficient uptake of 5-HT in vitro (Lesch et al. 1996; Greenberg et al. 1999). The S-allele has been found to be a risk variant in numerous anxiety disorders, and has also been found to moderate the effect of childhood abuse on depression, although not all studies are in agreement (Fergusson et al. 2011).

Recently, Hu et al. (2006) identified a single nucleotide polymorphism (SNP), rs25531, situated near the *5-HTTLPR* variant. This SNP has been reported to affect *SLC6A4* transcriptional activity, given that an AP2 transcription factor binding site is created by the rs25531 G-variant. In addition, rs25531 has been found to modulate the functionality of the L-allele: the L-G haplotype results in reduced *SLC6A4* expression (comparable to that of the S-allele), whilst the L-A haplotype is associated with increased *SLC6A4* expression (Hu et al. 2006) and increased *SLC6A4* binding potential in the putamen (Praschak-Rieder et al. 2007). Many researchers, therefore, have indicated that it is functionally more sound to group subjects who carry the L-G haplotype with those carrying S-alleles. This is particularly important in populations with African ancestry, as the frequency of the L-G haplotype has been found to be much higher than in other populations (Enoch et al. 2013).

Thus far, two studies have investigated the role of *5-HTTLPR* and rs25531 polymorphisms in AS, with contradictory results. Stein et al. (2008) reported on a significant association between S-allele homozygotes and increased levels of AS (on the physical concerns subscale). However, this association was only evident in individuals who had experienced high levels of childhood maltreatment, pointing to the role of a G × E interaction. However, Klauke et al. (2011) reported

a significant association between individuals homozygous for the long allele (LL or L-A/L-A) and increased levels of AS, in those who scored high on the childhood trauma (CT) scale.

Although variations in the 5' untranslated region (UTR) of *SLC6A4* have been widely investigated in psychiatric disorders in general, recent studies indicate a functional role for variants in the 3'UTR. In particular, rs3813034 is situated in one of the two polyadenylation sites thought to regulate *SLC6A4* gene expression (Battersby et al. 1999). The rs3813034 C-allele has been found to alter the fraction of *SLC6A4* carrying the distal polyadenylation signal, and this allele has been found to be associated with panic disorder (Gyawali et al. 2010) as well as impaired retention/consolidation of fear extinction memory and increased levels of trait anxiety and depression (Gyawali et al. 2010; Hartley et al. 2012). Another SNP in the 3'UTR, rs1042173, found to be in linkage disequilibrium (LD) with rs3813034, has been associated with alcohol abuse and craving (Seneviratne et al. 2009; Ait-Daoud et al. 2012). Evidence for rs1042173 functionality has been reported, with the C-allele found to disrupt the first nucleotide of a conserved binding site for has-miR-590-3p, resulting in increased *SLC6A4* expression (Seneviratne et al. 2009; Montasser et al. 2014). Finally, a SNP located in exon 2 of *SLC6A4*, rs6354, has been found to be associated with neuroticism, anxiety and depression and early-onset depression (Wray et al. 2009). However, no functionality has been assigned to the SNP as yet.

Adolescence has been found to be a period of intense psychological and physical change, with intensification of emotions and hypersensitivity to mild stressors (Casey et al. 2010). Profound remodelling of the serotonergic system has been observed during adolescence (Crews et al. 2007; Olivier et al., 2011; Klomp et al. 2012), and developmental stage has been found to moderate the effect of *SLC6A4* genotype in the brain (Ansorge et al. 2004, 2008). Indeed, it has been suggested that the effect of *5-HTTLPR* may be driven by its influence on neurodevelopment (Kobiella et al. 2011). Functional variants within *SLC6A4* may, therefore, alter the trajectory of the development of the emotional system during adolescence (Sakakibara et al. 2014), with the result that adolescents possessing susceptibility genotypes may be more vulnerable to developing psychopathology at a later stage.

Given the paucity of data on both 5' and 3'UTR *SLC6A4* variants and AS in adolescents, we thought it pertinent to investigate the role that both 5' and 3' variants may play in AS in the context of CT, in an adolescent, school-going South African study group.

Materials and methods

Participants

A representative selection of secondary schools ($n = 29$) was used in order to recruit 1149 participants. The clinical data pertaining to this dataset has previously been published (Martin et al. 2014). DNA was extracted from 985 (85.7%) participants, and it is this subset that is reported on here. Of the 985 participants, 634 (64.4%) self-classified as "Black, Xhosa-speaking", 317 (32.2%) self-classified as "Coloured (Mixed Ancestry)", 21 (2.1%) were Caucasian ("White"), 12 (1.2%) classified themselves as "Other", and one participant (0.1%) self-classified as "Asian". Participants classifying themselves as "White", "Other" or "Asian" were excluded from the analysis, resulting in a total of 951 participants. For clarity, the Black, Xhosa-speaking group will be referred to as "Xhosa" from this point onwards.

Permission to access secondary schools was provided by the Western Cape Education Department and the Health Research Ethics Committee at Stellenbosch University provided ethical approval.

Clinical measures

Each participant was administered the following clinical questionnaires:

The Child Anxiety Sensitivity Index (CASI; Silverman et al. 1991) is an 18-item self-report questionnaire designed for use in children and adolescents. Fear of anxiety is measured on a three-point scale by asking participants to rate the extent to which they believe the experience of anxiety will result in negative consequences.

The State-Trait Anxiety Inventory (STAI; Spielberger 1973) is a 40-item self-report questionnaire divided into two sections which assess both state and trait anxiety. For the current study, only the trait version of the scale was used.

The Childhood Trauma Questionnaire (CTQ; Bernstein and Fink 1998) is a 28-item retrospective measure of the frequency and severity of abuse and neglect experienced prior to age 18. The CTQ consists of five subscales that assess emotional, physical, and sexual abuse and emotional and physical neglect. Total scores range from 25 to 125, with scales for each trauma subtype ranging between 5 and 25. For the purpose of the proposed study, we enquired about maltreatment experienced prior to age 12.

The Center for Epidemiological Studies Depression Scale for children (CES-DC; Weissman et al. 1980) is a 20-item self-report measure of depression symptoms experienced during the past week.

The Alcohol Use Disorders Identification Test (AUDIT; Babor et al. 2001) is a 10-item self-report measure used to identify hazardous and harmful patterns of alcohol consumption in the past year.

The Connor-Davidson Resilience Scale (CD-RISC; Connor and Davidson 2003) is a 25-item self-report measure that assesses the level of stress coping ability over the past month.

Adolescent Coping Orientation for Problem Experiences (A-COPE; Patterson and McCubbin 1987) is a 54-item self-report coping inventory used to measure the behaviours and patterns that adolescents find helpful in managing problems or difficult situations.

Genotyping

Genomic DNA was extracted from saliva collected in Oragene™ DNA self-collection kits (OG-500, DNA Genotek, Ontario, Canada) using the Prep-It L2P reagent (DNA Genotek) as per manufacturer's instructions. The *5-HTTLPR* and rs25531 polymorphisms were genotyped by employing a two-stage genotyping procedure, as previously published (Voyiaki et al. 2009). The SNPs rs6354, rs1042173 and rs3813034 were genotyped using the Sequenom® iPLEX® Gold Genotyping Technology at The McGill University and Génome Québec Innovation Centre (Montreal, Canada).

Statistical analysis

Demographic and clinical characteristics were summarised as means and standard deviations, if approximately normally distributed, and as medians and ranges if non-normally distributed. Differences between groups (gender, ethnicity) were assessed using unadjusted linear models, transforming traits to normality where necessary. Subscales of the CTQ total were summarised by categorising the scores, and reporting number (%) within each category. Genotype counts (%) and Hardy-Weinberg equilibrium (HWE) P values were summarised separately for Xhosa and Coloured participants.

General linear modelling was used to express CASI total score (AS) as a function of a genotype, additive allelic or haplotype variable, adjusting for possible confounders by including them in the models. For association testing, the confounders were age, gender, depression (CESD total score), resilience (CD-RISC total score), coping mechanisms (A-COPE total score), trait anxiety (STAIT total score), alcohol use disorders (AUDIT total score) and CT (CTQ total score). Genotypes were coded as three categories (two degrees of freedom test), alleles were coded as the number of minor alleles (0, 1, 2), and each haplotype was similarly coded as number

present. Haplotypes were only inferred in the blocks constructed using the solid spine of LD method, implemented in Haploview software (version 4.2) (Barrett et al. 2005) and were investigated additive models only.

All modelling was done separately for the different ethnic groups (Coloured and Xhosa). When significant effects were detected ($P < 0.05$), dominant and recessive minor allele models were investigated as possible inheritance models, and gender effects were analysed. The best of the four possible models (smallest P value) was used to estimate the effects reported. The association effects were reported as the estimated mean difference in CASI total score between the specific genetic (genotypic, allelic or haplotype) factor, and the reference genetic factor. The effect sizes and their 95% confidence intervals were derived from the general linear models.

The interaction effects were represented by the differences between the slopes of the CASI \times CTQ lines between the specific genetic factor and the reference factor. Interaction tests were adjusted for the interaction between CTQ total score and the genetic factor under investigation with each of age at interview, gender, CESD total score, CD-RISC total score, A-COPE total score, STAIT total score, and AUDIT total score, by including them in the models.

Effects corresponding to P values below 5% were described as significant, except for the HWE tests, where 1% was the critical P value. All analyses were done using functions from R (R Development Core Team, 2012), and packages *genetics* (Warnes et al. 2013), *haplo.stats* (Sinnwell and Schaid 2015) and *effects* (Fox 2003).

Results

Demographic and clinical variables

All clinical and demographic statistics were measured separately for the Xhosa and Coloured study groups (Table 1). In total, there were 634 (259 [40.8%] male; 375 [59.2%] female) Xhosa, and 317 (129 [40.7%] male; 188 [59.3%] female) Coloured participants. The mean age at interview was 16.4 years ($SD = 2.1$ years) for Xhosa participants and 15.8 years ($SD = 1.6$ years) for Coloured participants, with no significant difference in age between male and female participants in either ethnic group ($P = 0.908$ and $P = 0.942$ in Xhosa and Coloured participants, respectively) (Table 1).

CTQ total scores were significantly different between Xhosa and Coloured participants ($P = 0.024$), with Xhosa participants exhibiting higher CTQ total scores (Table 1). Table 2 provides a summary of the frequency of self-reported

Table 1. Demographic and clinical characteristics of the study group, according to self-reported ethnicity and gender, and summarised as mean (SD) or median (range).

Clinical/demographic characteristic	Xhosa (67%)			Coloured (33%)		
	Female	Male	All	Female	Male	All
Number	375 (59%)	259 (41%)	634	188 (59%)	129 (41%)	317
Age (years), mean (SD)	16.4 (2.1)	16.4 (2.0)	16.4 (2.1)	15.8 (1.7)	15.80 (1.5)	15.8 (1.6)
CASI total, mean (SD)*	36.9 (6.2)	34.9 (6.2)	36.1 (6.3)	35.8 (6.6)	31.53 (6.3)	34.1 (6.8)
STAIT, mean (SD)*	47.3 (8.3)	45.9 (6.6)	46.7 (7.6)	46.8 (9.4)	42.05 (8.7)	44.8 (9.4)
CES-DC, mean (SD)	23.9 (11.1)	21.8 (10.3)	23.0 (10.8)	27.0 (12.4)	20.03 (11.9)	24.1 (12.6)
CD-RISC, mean (SD)*	57.3 (18.9)	57.0 (19.7)	57.2 (19.2)	64.7 (17.6)	62.87 (18.8)	64.0 (18.1)
A-COPE, mean (SD)	166.5 (20.3)	166.6 (23.1)	166.6 (21.5)	168.27 (22.3)	166.07 (22.4)	167.4 (22.4)
CTQ Total, median (range)*	43 (25 – 90)	44 (25 – 94)	43 (25 – 94)	40 (25 – 96)	39 (25 – 85)	40 (25 – 96)
AUDIT Total, median (range)*	0 (0 – 29)	0 (0 – 28)	0 (0 – 29)	1 (0 – 32)	2 (0 – 27)	2 (0 – 32)

CASI, Childhood Anxiety Sensitivity Index; CTQ, Childhood Trauma Questionnaire; STAIT, State-Trait Anxiety Inventory; CES-DC, Center for Epidemiological Studies Depression Scale for children; AUDIT, Alcohol Use Disorders Identification Test; CD-RISC, Connor-Davidson Resilience Scale; A-COPE, Adolescent Coping Orientation for Problem Experiences.

*Indicates significant differences between the Xhosa and Coloured groups ($P < 0.05$).

Table 2. Counts and percentages of CT reported by OCD participants.

Type of childhood trauma	Group	Severe to extreme	Moderate to severe	Low to moderate	None or minimal
Emotional abuse*	Xhosa	48 (7.57)	67 (10.57)	178 (28.08)	341 (53.79)
	Coloured	46 (14.5)	44 (13.9)	89 (28.1)	138 (43.5)
Emotional neglect*	Xhosa	107 (16.9)	107 (16.9)	191 (30.1)	229 (36.1)
	Coloured	26 (8.2)	38 (12.0)	92 (29.0)	161 (50.8)
Physical abuse	Xhosa	93 (14.7)	69 (10.9)	88 (13.9)	384 (60.6)
	Coloured	33 (10.41)	25 (7.89)	43 (13.56)	216 (68.14)
Physical neglect*	Xhosa	136 (21.5)	127 (20.0)	129 (20.3)	242 (38.2)
	Coloured	36 (11.4)	39 (12.3)	62 (19.6)	180 (56.8)
Sexual abuse	Xhosa	54 (8.52)	106 (16.72)	104 (16.40)	370 (58.36)
	Coloured	31 (9.78)	41 (12.93)	38 (11.99)	207 (65.30)

Counts represent low to extreme CT, using threshold values for each type of CT as per Bernstein and Fink (1998).

*Indicates significant differences ($P < 0.05$) between Xhosa and Coloured groups.

CT for each of the CTQ subscales (Bernstein and Fink 1998). Childhood emotional neglect was found to be the most prominent form of abuse reported by the Xhosa adolescents (63.9% reported low to extreme forms of emotional neglect (i.e. low, moderate, severe or extreme forms of neglect)), followed by physical neglect (61.8% reported low to extreme forms of physical neglect). Coloured adolescents reported childhood emotional abuse most often (56.5% reported low to extreme forms of emotional abuse), followed by emotional neglect (49.2% reported low to extreme forms of emotional neglect).

Genetic variables

All variants were in HWE ($P > 0.01$) in both ethnic groups. Genotype distribution summaries for the variants are provided in Table 3.

No statistically significant association was observed between genotype and AS in the Xhosa group; however, a significant association was detected between *5-HTTLPR* and AS in the Coloured sample ($P = 0.046$). This association, detected using the recessive inheritance model, was detected only in Coloured males ($P = 0.016$). Coloured males homozygous for the *S*-allele had CASI total scores that were an estimated 3.73 (95% CI: 0.72–6.74) higher than Coloured males with *LL* and *LS* genotypes.

In the Xhosa group, a significant interaction effect ($P = 0.037$) was detected between *rs1042173* (recessive inheritance model) and CTQ total score on CASI total score, adjusted for the relevant confounders, as listed in the Methods section. CASI total score decreased for each unit increase in CTQ total score for *CC* homozygotes and

for individuals possessing at least one *A*-allele (*AA*+*AC*). However, the decrease in CASI total score occurred at a significantly greater rate in *CC*-homozygous individuals; the difference in the slopes between *CC* and *AA*+*AC* genotype groups was -0.32 (95% CI: -0.61 to -0.02) (Figure 1). This significant interaction was not found to be gender-specific ($P = 0.629$ in Xhosa males and $P = 0.896$ in Xhosa females).

No significant interaction effects were detected between CTQ total score and any of the genetic variants on CASI total score among Coloured adolescents.

We detected one haplotype block (*5-HTTLPR*-*rs25531*) in the Xhosa sample (Figure 2A), and two haplotype blocks in the Coloured sample (Figure 2B).

A significant association was detected between the *5-HTTLPR*-*rs25531* haplotype and AS among Xhosa adolescents, after adjusting for confounders. Each copy of the *L-G* haplotype, carried by a Xhosa adolescent, protects against an estimated mean increase of 1.29 in CASI total score, compared to the *L-A* haplotype ($P = 0.010$) (Table 4). When stratified by gender, no association was observed within either the male ($P = 0.177$) or female ($P = 0.071$) groups.

No significant associations were detected between either of the haplotype blocks and AS among Coloured adolescents. In addition, no significant interactions were detected between either of the haplotype blocks and CTQ on the AS in either of the ethnic groups.

Discussion

This study investigated the role that variants at the 5' and 3' ends of the *SLC6A4* gene play in AS in a cohort of

Table 3. Genotype counts and frequencies (%) of *SLC6A4* variants, stratified by gender.

Variant	Genotype	Xhosa		HWE <i>P</i> value	Coloured		HWE <i>P</i> value
		Female	Male		Female	Male	
rs25531	AA	253 (73.5)	180 (74.4)	0.614	140 (78.7)	86 (77.5)	0.568
	AG	87 (25.3)	53 (21.9)		36 (20.2)	22 (19.8)	
	GG	4 (1.2)	9 (3.7)		2 (1.1)	3 (2.7)	
	Total	344	242				
<i>5-HTTLPR</i>	LL	171 (49.7)	122 (50.4)	0.013	73 (41.0)	53 (47.7)	0.518
	LS	151 (43.9)	109 (45.0)		80 (44.9)	46 (41.4)	
	SS	22 (6.4)	11 (4.5)		25 (14.0)	12 (10.8)	
	Total	344	178				
rs3813034	AA	253 (73.3)	179 (70.8)	1.000	77 (44.0)	49 (43.8)	0.138
	AC	86 (24.9)	67 (26.5)		80 (45.7)	57 (50.9)	
	CC	6 (1.7)	7 (2.8)		18 (10.3)	6 (5.4)	
	Total	345	175				
rs1042173	AA	267 (71.6)	178 (69.0)	0.660	83 (45.6)	52 (42.6)	0.189
	AC	96 (25.7)	72 (27.9)		81 (44.5)	62 (50.8)	
	CC	10 (2.7)	8 (3.1)		18 (9.9)	8 (6.6)	
	Total	373	182				
rs6354	AA	143 (39.0)	78 (30.7)	0.802	96 (53.0)	67 (54.9)	0.884
	AC	158 (43.1)	138 (54.3)		74 (40.9)	44 (36.1)	
	CC	66 (18.0)	38 (15.0)		11 (6.1)	11 (9.0)	
	Total	367	181				

P values are from exact tests of Hardy–Weinberg equilibrium.

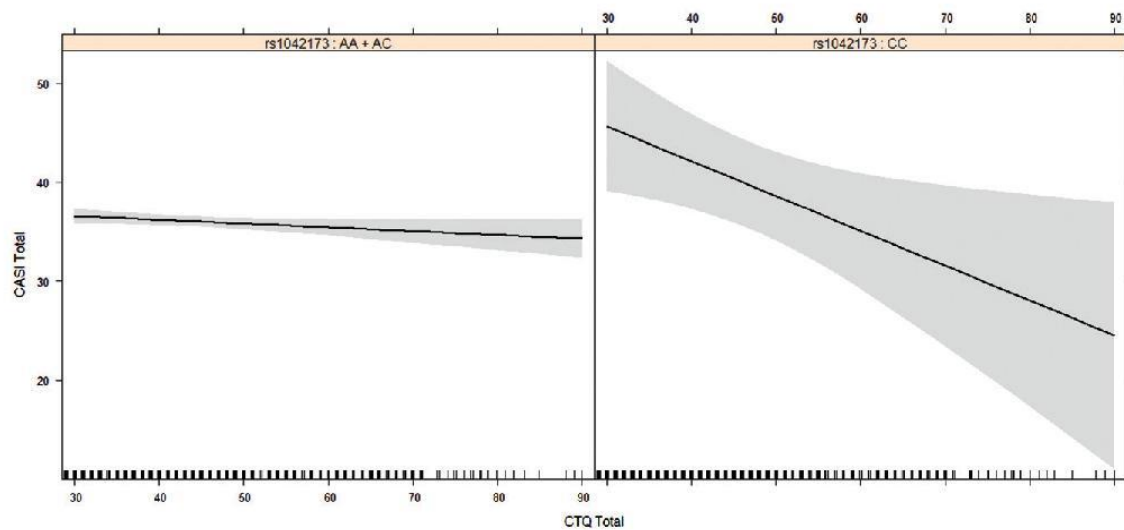


Figure 1. Interaction ($P = 0.037$) between CT (CTQ total score) and the rs1042173 recessive inheritance model on AS (CASI total score) in the Xhosa group, after adjusting for confounders. The plots show the association between CT and AS in Xhosa participants who possess at least one A-allele (left graph) and those who are homozygous for the C-allele (right graph). Shaded areas represent the 95% confidence intervals. The interaction effect is the difference between the slopes of the lines (-0.32 [95% CI: -0.61 to -0.02]).

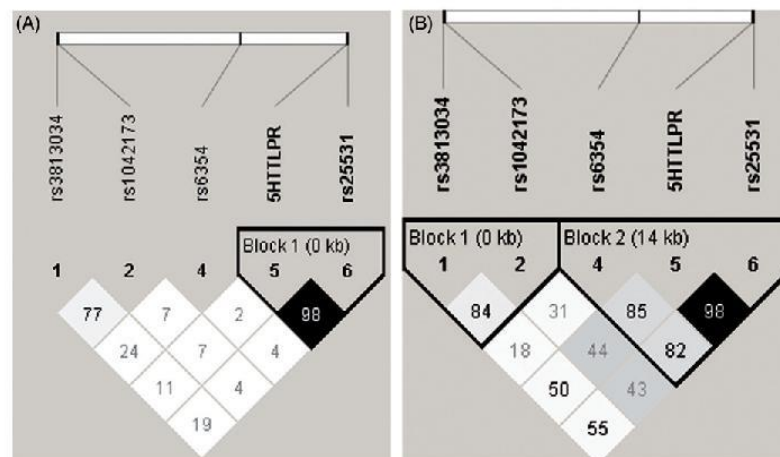


Figure 2. Linkage disequilibrium map for the (A) Xhosa and (B) Coloured participants. D' values are depicted in the diamonds, with darker colours depicting stronger LD. The LD map was created using the solid spine of LD, implemented in Haploview (Barrett et al. 2005).

South African adolescents, as it has been hypothesised that variants at either end of the gene could exert independent effects on psychopathology (Enoch et al. 2013). To the best of our knowledge, this is the first study to investigate the role of 5' and 3' variants in *SLC6A4* in AS in a South African adolescent population.

Xhosa and Coloured adolescents were analysed separately to eliminate the possible effects of population stratification. In Coloured males, the 5-HTTLPR S-allele was found to be associated with increased AS under the

recessive model. S-allele carriers are hypothesised to be at increased risk for development of anxiety disorders, given their reduced *SLC6A4* expression, fewer 5-HT1A receptors and an exaggerated hypothalamic pituitary adrenal axis response to stress (Li 2006). In addition, the S-allele has been associated with neuroticism (an anxiety-related trait) (Lesch et al. 1996), increased amygdalar response to emotional stimuli (in psychiatrically healthy individuals) (Murphy et al. 2013) and bias towards negative stimuli (Pergamin-Hight et al. 2012). Given the evidence for an

Table 4. Summary of 5-HTTLPR-rs25531 haplotype association ($P = 0.011$) with AS in the Xhosa group.

5-HTTLPR	rs25531	Haplotype frequency	Effect	95% CI		P value
				Lower	Upper	
S	A	0.29	-0.31	-1.05	0.44	0.419
L	G	0.12	-1.29	-2.28	-0.31	0.010**
S	G	0.01	2.23	-1.40	5.85	0.229
L	A	0.58*	0	-	-	-

Effect is the estimated difference in mean CASI total score between having the specific haplotype and the reference, L-A, haplotype.

*Reference haplotype frequency.

**Significant association ($P < 0.05$).

Abbreviation: CI, confidence interval.

association between the S-allele and increased AS, it is interesting to note that, in the Xhosa sample, the 5-HTTLPR-rs25531 L-G haplotype, compared to the L-A haplotype, was found to be *protective* against high levels of AS. The L-G combination has been reported to possess functionality similar to the S-allele (Hu et al. 2006) therefore, if the association is based on putative functionality of the variants, we would expect the L-G haplotype to represent a risk haplotype in Xhosa adolescents. Our apparently contradictory results may potentially be explained by the differing genetic architecture between the Xhosa and Coloured populations. Indeed, the direction of association of *SLC6A4* with amygdala reactivity has been found to be population-specific (Munafò et al. 2008). For example, increased amygdala activity and reduced functional coupling between the prefrontal cortex (PFC) and amygdala has been reported in L-carriers of Asian or East African ancestry (Munafò et al. 2008; Long et al. 2013), while the S-allele has been associated with reduced PFC-amygdala connectivity in Caucasians (Caspi et al. 2003). Alternatively, it is possible that the 5-HTTLPR variant is associated with AS by virtue of epistatic interactions which occur between it and the true risk variant, which may be in LD with alternate 5-HTTLPR-rs25531 alleles in different populations. The present finding thus underscores the importance of not accepting significant associations at face value, but investigating and replicating the relevant genetic variants in populations of differing ethnicity.

In the Xhosa group, a gene-environment ($G \times E$) interaction on AS was observed for the rs1042173 CC-genotype, which was found to modify the association between AS and CT by acting to protect against increased AS, as CT increased. The minor C-allele of rs1042173 has been found to disrupt the first nucleotide of a conserved binding site for microRNA has-miR-590-3p (Montasser et al. 2014), which should, theoretically, result in increased levels of *SLC6A4* mRNA and protein. Indeed, functional studies conducted by Seneviratne et al. (2009) found that the C-allele yielded significantly

increased levels of *SLC6A4* mRNA and protein expression, although results to the contrary have also been published (Vallender et al. 2008). Increased levels of *SLC6A4* would result in an initial reduction in the amount of serotonin available for neurotransmission; however, the lack of serotonin should activate a feedback mechanism in the presynaptic autoreceptor neurons, triggering the consequent production of serotonin (Seneviratne et al. 2009; Montasser et al. 2014). Individuals possessing the CC-genotype may thus produce more serotonin than those possessing the A-allele, possibly protecting them against the adverse effects of early CT. It is interesting that the rs1042173, in the 3' region of the gene, and the 5-HTTLPR and rs25531 variants, in the 5' region of the gene, exhibit clear differences regarding interaction with the environment and the subsequent moderation of association with AS. Independent effects of variants in the 5' and 3' regions of *SLC6A4* have been reported on previously (Enoch et al. 2013), and results obtained in the present study highlight the necessity of including variants in the 3' region of the gene when analysing the genetic basis of psychiatric disorders.

Jang et al. (1999) reported that AS was only heritable in females, and other groups have reported female-dominated effect of the 5-HTTLPR L-allele in AS (Klauke et al. 2011), however, we only observed the role of gender when investigating the association between 5-HTTLPR S-allele and AS in Coloured males. The male-specific association between the S-allele and anxiety or anxiety-related traits has been reported on before (Du et al. 2000). Males homozygous for the S-allele have been found to possess lower levels of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) (a marker of 5-HT turnover) compared to females (Williams et al. 2003) therefore, females with at least one S-allele may possess higher serotonergic function than their male counterparts (Wang et al. 2014), which may act as a buffer against increased levels of AS. However, future studies are required to replicate and probe the mechanisms underlying the gender-specific effects of the 5-HTTLPR variant.

Limitations

The present study yields interesting findings in a novel setting; however, there are certain limitations that merit mention. First, we did not correct for population stratification in either the Coloured or the Xhosa sample groups. The Xhosa population originated from West Africa approximately 3000 to 5000 years ago (Lane et al. 2002) and now occupy large regions of the Eastern Cape in South Africa. The population is currently the second-largest ethnic group in the country, constituting

approximately 18% of the South African population (Drögemöller et al. 2010). Although no in-depth analysis has been performed to study the underlying genetic substructure in the Xhosa population, the linguistic subgroup to which they belong (Niger-Kordafarian group) has been found to exhibit relative genetic homogeneity (Tishkoff et al. 2009; Bryc et al. 2010; Veeramah et al. 2012). In addition, the Xhosa population is characterised by cultural and ethnic isolation and thus less likely to present with genetic and phenotypic heterogeneity (Niehaus et al. 2005). On the other hand, the South African Coloured population has been found to have some of the highest levels of admixture globally (Tishkoff et al. 2009). The population comprises Khoesan, Bantu-speaking (including Xhosa), European and Asian ethnicity, and as a result of the diverse ancestral origin of the population, we would expect a fair amount of genetic heterogeneity, which could confound results in this study group. The confounding effect of population stratification could partially explain the reasons for the lack of association observed between *SLC6A4* and AS within the Coloured population in the present study. Therefore, caution should be taken when interpreting the results from the Coloured sample. Future studies should incorporate robust measures for correcting for population stratification in this population.

The second limitation pertains to the use of the CTQ as an instrument to assess CT. Although a reliable and validated means of trauma assessment (Bernstein and Fink 1998), the CTQ is a retrospective, self-report assessment and may be vulnerable to a number of biases, including recall bias. Finally, we did not apply any correction for multiple tests, primarily due to the exploratory nature of the study. The most appropriate means of correcting for multiple testing remains contentious, and applying Bonferroni's correction may be too conservative in cases where there is prior evidence that such associations may be present. Given these limitations, the results presented should be interpreted with caution until such time as they are replicated in a scientifically rigorous manner.

Conclusions

In conclusion, this study extends and adds to the growing literature on the role of the serotonin transporter in the development of anxiety disorders and anxiety-related traits. First, we investigated not only the widely studied *5-HTTLPR* polymorphism in the gene's 5' region, but also the less widely investigated polymorphisms closer to the 3' end of the gene; second, we focussed on the less widely studied Xhosa and Coloured populations of South Africa. The present

study highlights the role that *SLC6A4* plays in anxiety-related disorders, at the same time highlighting the possibility that the 5' and 3' ends of the gene possess the ability to independently and differentially affect the levels of AS within our South African cohort. Future studies are required to replicate the results of the present study.

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Statement of interest

None to declare.

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APPENDIX A2:

Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth?



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Research report

Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth?

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ABSTRACT

Background: Stressful life events in adolescents have been found to be longitudinally associated with higher anxiety sensitivity (AS). A question that has not been addressed is whether AS in adolescence is associated with different childhood adversity exposures.

Methods: School attending adolescents ($n = 1149$) completed measures of anxiety sensitivity (CASI), trait anxiety (STAI-T), childhood trauma (CTQ), depression (CES-DC), alcohol (AUDIT) and drug use (DUDIT), and resilience (CD-RISC) and coping orientation (A-COPE).

Results: There was no significant gender difference in childhood trauma exposure, resilience levels or coping orientation. Gender differences were evident in terms of AS, trait anxiety, depression, alcohol and drug use. Depression, trait anxiety and alcohol use mediated the relationship between the amount of childhood trauma and AS and played a role in the relationship between certain childhood trauma types and AS. Neither resilience nor coping orientation had a moderating effect on the relationship between the amount of childhood trauma and AS.

Limitations: Cross-sectional study, over- or under-reporting of data due to use of self-report instruments, and use of a retrospective measure of childhood trauma (CTQ) that is subject to recall bias.

Conclusions: Girls are at greater risk than boys for early onset anxiety disorders as girls have higher rates of AS, trait anxiety and depression despite the same rates of childhood trauma, coping orientation and resilience. Our findings, in the context of childhood trauma, underscore the influence of depression, trait anxiety and alcohol use as risk factors for the development of AS in youth.

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1. Introduction

Anxiety disorders are one of the most frequently diagnosed conditions among adolescents (Kessler et al., 2012) with lifetime rates for “any anxiety disorder” in the order of 15–20% (Beesdo et al., 2009). Data from twin studies indicate that both genetic influences and environmental effects substantially contribute to the variance in anxiety symptoms (Topolski et al., 1997) and anxiety-related temperamental traits, such as, trait anxiety (Legrand et al., 1999) and anxiety sensitivity (AS) (Stein et al., 1999). AS and trait anxiety are commonly elevated in individuals with anxiety disorders in comparison with non-clinical controls (Olatunji and Wolitzky-Taylor, 2009; Kiliç et al., 2008).

AS and trait anxiety are empirically and conceptually distinct (McNally, 1996). AS is considered a dispositional characteristic

(McNally, 2002) and an established cognitive risk factor for the development of anxiety in children and adolescents (McLaughlin and Hatzenbuehler, 2009). AS refers to the fear of anxiety-related bodily sensations and symptoms based on the individual's beliefs that these sensations and symptoms have harmful physical, psychological and/or social consequences (Reiss, 1991; Reiss and McNally, 1985) and these fears are thought to intensify pre-existing anxiety (Reiss, 1991). Trait anxiety denotes the tendency to respond fearfully to stressors in general (McNally, 1989) and has been shown to uniquely predict PTSD symptoms and generalised anxiety disorder symptoms in traumatised children and youths (Hensley and Varela, 2008; Weems et al., 2007). Significantly higher levels of trait anxiety have been reported in adult outpatients with histories of childhood physical and sexual abuse in comparison with non-abused outpatients (Handa et al., 2008). Moreover, there is evidence for the onset and persistence of psychopathology due to adversities experienced in childhood, as these are associated with adolescent and adult psychopathology (Benjet et al., 2010; Clark et al., 2010). Individuals with histories of early life stressor exposure have been shown to have significantly

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higher anxiety and depression symptom scores, in comparison with those without such histories (Chu et al., 2013). Childhood maltreatment and adversity is also associated with greater drug and alcohol use (Arata et al., 2007; Danielson et al., 2009), and in adolescents, childhood adversity is associated with the opportunity to use alcohol, alcohol use and alcohol abuse/dependence and illicit drugs, actual drug use, and drug abuse and dependence (Benjet et al., 2013). Danielson et al. (2009) found that over 60% of adolescents with past-year abuse or dependence of alcohol, marijuana, and/or other hard drugs, reported a history of childhood physical and/or sexual assault.

In a community sample of adolescents, McLaughlin and Hatzenbuehler (2009) found that stressful life events (i.e. stressors related to health and family discord) were significantly associated with anxiety symptoms at follow-up and were also shown to be longitudinally associated with increases in AS (McLaughlin and Hatzenbuehler, 2009). Childhood emotional maltreatment has been reported to be associated with higher levels of AS in young adults, with parental threatening behaviour playing the strongest role in predicting overall AS (Scher and Stein, 2003). These findings highlight the role of environmental factors in the development of AS.

Taken together, it appears reasonable that childhood trauma, shown to be associated with anxiety and depressive symptoms (Hovens et al., 2010), could be an important risk factor for increased levels of AS. To better understand the factors that contribute to AS, we investigated the role of childhood trauma amount and type (i.e. emotional, physical and sexual abuse; and emotional and physical neglect) in the prediction of AS; and the role of protective (i.e. resilience and coping) and risk (i.e. trait anxiety, depression, alcohol and drug use) factors as moderators and mediators, respectively, in this relationship.

2. Methods

2.1. Participants

Participants comprised 1149 randomly selected school-attending youths from a representative sample of secondary schools ($n=29$) from Cape Town, South Africa. The mean age of the sample was 16.24 years (range = 13–23, $SD=1.95$). The majority were girls (689/1149, 59.97%) and the mean level of education was grade 9 (range = 8–12, $SD=1.30$). Most youths identified themselves as Black (68.9%, 792/1149).

2.2. Procedure

Permission to access secondary schools was provided by the Western Cape Education Department and the Health Research Ethics Committee at Stellenbosch University provided ethical approval. Secondary schools were randomly selected from all public schools in Cape Town. These schools were approached and those that agreed to participate were requested to provide names of all learners from grades 8 to 12. Thereafter, a sample of 20 learners per grade was randomly selected from the list of learners' names issued by the individual schools. Written informed consent was obtained from parents/guardians and written assent was obtained from the learners themselves, who were then administered study questionnaires. This was completed at the schools, on a single occasion, at a time indicated by the school head.

2.3. Measures

The Childhood Anxiety Sensitivity Index (CASI, Silverman et al., 1991) is an 18-item self-report questionnaire designed for use with

school-age children and adolescents. The CASI measures the fear of anxiety on a 3-point scale by asking participants to rate the extent to which they believe the experience of anxiety will result in negative consequences, comprising physical, psychological and social concerns. The CASI has a range of 18–54 with higher scores reflecting higher levels of AS. In the current study, the CASI had good internal consistency ($\alpha=0.81$).

The State-Trait Anxiety Inventory (STAI, Spielberger, 1973). The trait version of the STAI is a 20-item self-report measure that assesses an individual's trait anxiety (i.e. the tendency to respond fearfully to stressors in general) (McNally, 1989) and thus participants are asked to respond to the items in terms of how they generally feel. Items are rated on a 4-point scale and scores can range between 20 and 80, with higher scores reflecting higher levels of trait anxiety (Spielberger, 1973). Internal consistency of the STAI-T in the current study was relatively poor ($\alpha=0.62$).

The Childhood Trauma Questionnaire (CTQ, Bernstein and Fink, 1998) is a 28-item retrospective self-report measure of the frequency of and severity of different types of childhood trauma, namely, abuse (i.e. emotional, physical and sexual) and neglect (i.e. emotional and physical) experienced prior to the age of 18. Participants respond to each item in the context of "when you were growing up" and answer according to a 5-point Likert scale. CTQ scores can range from 25 to 125, with scores for each trauma scale (i.e. emotional, physical and sexual abuse and emotional and physical neglect) ranging from 5 to 25. The CTQ also includes a 3-item Minimisation/Denial scale that indicates the potential underreporting of maltreatment (Bernstein and Fink, 1998). Internal consistency in the current study for the CTQ total was good ($\alpha=0.86$) and ranged from $\alpha=0.53$ (physical neglect subscale) to $\alpha=0.80$ (sexual abuse subscale) for the CTQ trauma types.

The Centre for Epidemiological Studies Depression Scale for Children (CES-DC, Faulstich et al., 1986; Weissman et al., 1980) is a 20-item self-report measure of past week depressive symptoms. Items are rated on a 5-point scale (scores ranging from 0 to 60) with higher scores indicating increasing levels of depression. In the current study, the CES-DC had good internal consistency ($\alpha=0.87$).

The Alcohol Use Disorders Identification Test (AUDIT, Babor et al., 2001; Saunders et al., 1993) is a 10-item self-report measure used to identify hazardous and harmful patterns of alcohol consumption in the past year. Items are rated on a 5-point scale (score range 0–40). Higher scores are indicative of potential hazardous and harmful alcohol use. Internal consistency of the AUDIT in the current study was good ($\alpha=0.87$).

The Drug Use Disorders Identification Test (DUDIT, Berman et al., 2005) is an 11-item self-report measure (score range 0–44) used to identify drug use patterns and various drug-related problems, with higher scores indicative of possible drug-related problems. Internal consistency of the DUDIT in the current study was very good ($\alpha=0.89$).

The Connor-Davidson Resilience Scale (CD-RISC, Connor and Davidson, 2003) is a 25-item self-report measure that assesses the level of stress coping ability over the past month. Responses are coded on a 5-point Likert scale and the total score can range from 0 to 100 with higher scores indicating greater levels of resilience. Internal consistency of the CD-RISC in the current study was excellent ($\alpha=0.92$).

Adolescent Coping Orientation for Problem Experiences (A-COPE, Patterson and McCubbin, 1987) is a 54-item self-report coping inventory used to measure the behaviours and patterns that adolescents find helpful in managing problems or difficult situations. Responses to items are coded on a 5-point Likert scale. The total score can be used as an overall measure of coping and has a range of 54–270, with higher scores indicating better levels of coping behaviours and patterns. Internal consistency in the current study for the A-COPE was good ($\alpha=0.84$).

2.4. Data analyses

Descriptive statistics were computed for demographic and psychopathology data, with variables of interest including age, gender and ethnicity, as well as levels of childhood trauma, AS, trait anxiety, depression, and alcohol and drug problems. Boys and girls were compared on continuous variables using independent samples *t*-tests and on categorical variables using chi-square tests. Bivariate correlational analysis was conducted to determine the strength of associations between childhood trauma and AS, respectively, and risk and protective factor variables. In order to determine whether childhood trauma predicted AS, simple linear regression analysis was conducted. Multiple regression analyses was used to determine whether childhood trauma uniquely predicted childhood anxiety sensitivity, when controlling for trait anxiety, depression, alcohol and drug use and whether resilience and coping behaviour modified the aforementioned prediction. Thereafter, mediation analysis was conducted using the CTQ total and then the CTQ trauma types as independent variables and anxiety sensitivity total as the outcome variable. Potential mediators included depression, trait anxiety, alcohol and drug use. Sobel's tests of mediation were conducted to determine whether mediation effects were significant. Further analysis of these mediators was carried out using PLS structural equation modelling (PLS-SEM). Moderator analysis was used to determine whether protective factors (i.e. resilience and coping orientation) had significant moderating effects on AS. These analyses were conducted based on testing the effects of adding/removing interaction effects in regression analysis. A two-tailed $p < 0.01$ was considered statistically significant due to the large sample size. Data were analysed using SPSS version 21, STATISTICA version 12 and SmartPLS version 2.0.M3.

3. Results

3.1. Anxiety sensitivity and gender

Please see Table 1 for mean scores for all the risk/psychopathology variables for the total sample and the genders. Girls scored significantly higher than boys on the CASI [$t(1147) = -6.79, p < 0.01$], including on all CASI subscales: physical concerns [$t(1147) = -7.09,$

$p < 0.01$]; social concerns [$t(1147) = -2.91, p < 0.01$] and psychological concerns [$t(1015.53) = -4.99, p < 0.01$].

3.2. Childhood trauma and other risk/psychopathology variables

There were no significant gender differences in CTQ total mean score [$t(1147) = 0.59, p > 0.01$]. Girls scored significantly higher on trait anxiety [$t(1147) = -4.51, p < 0.01$] and depression [$t(1147) = -4.61, p < 0.01$]. Boys, in contrast, scored significantly higher on alcohol [$t(891.224) = 3.94, p < 0.01$] and drug use [$t(703.672) = 4.77, p < 0.01$].

3.3. Depression and problematic alcohol/drug use

73.6% (846/1149) of youths scored at or above the clinical cut-point of 16 or more on the CES-DC for depression, 77.2% (532/689) of girls and 68.3% (314/460) of boys [$\chi^2(1, N = 1149) = 11.39, p < 0.01$]. The effect size for this finding was small (Cramer's $V = 0.10$).

Almost 25% of the sample [23.3% (268/1149)] had a score of 8 or more on the AUDIT, indicative of hazardous/harmful alcohol use and possible alcohol dependence, with 29.1% (134/460) of boys and 19.4% (134/689) of girls [$\chi^2(1, N = 1149) = 14.46, p < 0.01$] in this category. The effect size for this association was small (Cramer's $V = 0.11$).

Based on a cut-off of 6 or more for males and 2 or more for females on the DUDIT, 14.3% (164/1149) of the total sample likely had drug-related problems, with 15.7% (72/460) of boys and 13.4% (92/689) of girls in this category, although the association with gender was non-significant [$\chi^2(1, N = 1149) = 1.19, p > 0.01$].

3.4. Resilience and coping

No significant gender differences on either the CD-RISC [$t(1147) = -0.43, p > 0.01$] or the A-COPE [$t(898.97) = -0.01, p > 0.01$] were evident.

3.5. Anxiety sensitivity, childhood trauma and other risk and protective factors

Significant correlations were evident between the CASI and the CTQ total score, CTQ emotional abuse subscale and CTQ physical abuse subscale. Furthermore, the CASI correlated significantly with

Table 1
Anxiety sensitivity, childhood trauma and other risk and protective factors (total sample and by gender).

Measure	Total (mean and SD) <i>n</i> = 1149	Males (mean and SD) <i>n</i> = 460	Females (mean and SD) <i>n</i> = 689	<i>p</i> -Value
CASI total	35.53 (6.52)	33.96 (6.41)	36.57 (6.39)	< 0.01
CASI physical concerns	20.20 (4.39)	19.10 (4.31)	20.94 (4.29)	< 0.01
CASI social concerns	10.10 (1.92)	9.90 (2.00)	10.24 (1.86)	< 0.01
CASI psychological concerns	5.22 (1.51)	4.96 (1.45)	5.40 (1.52)	< 0.01
CTQ total	45.32 (14.43)	45.63 (14.26)	45.12 (14.54)	<i>n.s.</i>
CTQ PN	8.99 (3.67)	9.14 (3.73)	8.90 (3.62)	<i>n.s.</i>
CTQ EA	9.48 (4.36)	9.21 (4.09)	9.66 (4.52)	<i>n.s.</i>
CTQ EN	11.70 (4.85)	11.87 (4.89)	11.59 (4.83)	<i>n.s.</i>
CTQ PA	8.05 (4.14)	8.25 (4.07)	7.91 (4.18)	<i>n.s.</i>
CTQ SA	7.10 (3.69)	7.16 (3.58)	7.07 (3.76)	<i>n.s.</i>
STAI-T	46.12 (8.09)	44.81 (7.46)	46.99 (8.39)	< 0.01
CES-DC	23.33 (11.43)	21.44 (10.87)	24.59 (11.62)	< 0.01
AUDIT	4.39 (6.58)	5.34 (7.06)	3.75 (6.17)	< 0.01
DUDIT	1.71 (4.67)	2.58 (5.78)	1.14 (3.66)	< 0.01
CD-RISC	59.10 (19.06)	58.80 (19.52)	59.29 (18.77)	<i>n.s.</i>
A-COPE	167.07 (21.69)	167.06 (23.29)	167.08 (20.57)	<i>n.s.</i>

Abbreviations: *n.s.*, non-significant; CASI, anxiety sensitivity; CTQ, childhood trauma; CTQ PN, physical neglect; CTQ EA, emotional abuse; CTQ EN, emotional neglect; CTQ PA, physical abuse; CTQ SA, sexual abuse; STAI-T, trait anxiety; CES-DC, self-reported depression; AUDIT, alcohol use; DUDIT, drug use; CD-RISC, resilience; A-COPE, coping orientation.

the STAI-T, the CES-DC, the AUDIT, the CD-RISC and the A-COPE. CTQ total scores were significantly correlated with all risk and protective variables, with small correlations being significant likely due to the large sample size (table available from the authors on request).

3.6. Regression analyses

3.6.1. CTQ total and other risk variables

On simple linear regression, CTQ total scores ($\beta=0.16$, $t(1147)=5.67$, $p<0.01$) positively and significantly predicted CASI scores ($R^2=0.03$, $F(1, 1147)=32.17$, $p<0.01$), accounting for 2.7% of the variance in AS. When other risk variables (depression, alcohol and drug use, and trait anxiety) were added to the model, the predictive ability of CTQ total on AS became significantly negative ($\beta=-0.10$, $t(1143)=-3.26$, $p<0.01$), indicating that the CES-DC ($\beta=0.29$, $t(1143)=8.88$, $p<0.01$), the STAI-T ($\beta=0.25$, $t(1143)=7.66$, $p<0.01$) and the AUDIT ($\beta=0.11$, $t(1143)=3.93$, $p<0.01$) were significant predictors of CASI scores, with the CES-DC and the STAI-T having the largest predictive ability on AS, based on their larger beta coefficients. DUDIT scores did not predict CASI scores ($\beta=-0.05$, $t(1143)=-1.82$, $p>0.05$). Inspection of the

redundancy table indicated that there was no multicollinearity between the variables as tolerance values were all well above 0.2.

3.6.2. Mediator effects: CTQ total and risk variables

Results from the PLS mediator model indicated that when risk variables were added to the model, the relationship between CTQ total and CASI scores became significantly negative (see Table 2). This indicated partial mediation, as the CTQ total had a positive influence on CASI through the CES-DC, STAI-T and DUDIT, but had a direct negative influence on CASI. Further investigation indicated that all path coefficients from childhood trauma to risk factor variables were all positive and significant and all path coefficients from risk factor variables to the CASI were positive and significant, with the exception of the path coefficient from the DUDIT to the CASI (see Fig. 1). These findings suggest that trait anxiety, depression and alcohol use have mediating effects between childhood trauma and AS. Based on their large and significant path coefficients, childhood trauma, in this model, was most strongly associated with depression and trait anxiety. Sobel's test results indicated that the indirect effect of trait anxiety on AS was significant ($IE=0.09$, $z=10.38$, $p<0.01$; IE lower 95% $CI=0.07$, upper 95% $CI=0.10$), as was the indirect effect of depression ($IE=0.09$, $z=10.52$, $p<0.01$; IE lower 95% $CI=0.07$, upper 95% $CI=0.10$) and alcohol use, though relatively small ($IE=0.01$, $z=3.77$, $p<0.01$; IE lower 95% $CI=0.01$, upper 95% $CI=0.02$). Based on the large coefficients of the CES-DC and the STAI-T, both from the CTQ and to the CASI, relative to the AUDIT, it appears that depression and trait anxiety have the strongest mediating effects.

3.6.3. Moderator analysis: CTQ total and protective variables

Results indicated that neither resilience ($\Delta R^2=-0.001$, $F_{\text{to remove}}=1.49$, $p<0.05$) nor coping orientation ($\Delta R^2=-0.001$, $F_{\text{to remove}}=1.27$, $p<0.05$) had a moderating effect on the relationship between the CTQ and the CASI.

3.6.4. CTQ trauma type and risk variables

All the variables in the multiple regression model, namely, CTQ trauma types (i.e. emotional, physical and sexual abuse, and emotional and physical neglect) and the CES-DC, the STAI-T, the

Table 2
Path coefficients: childhood trauma, anxiety sensitivity and other risk variables.

Path	Path coefficient	Bootstrap mean	95% lower CI	95% upper CI
CTQ → CASI	-0.11*	-0.11	-0.17	-0.04
CTQ → AUDIT	0.17*	0.18	0.11	0.24
CTQ → CES-DC	0.48*	0.48	0.43	0.53
CTQ → DUDIT	0.13*	0.13	0.07	0.2
CTQ → STAI-T	0.48*	0.48	0.43	0.52
CES-DC → CASI	0.28*	0.28	0.21	0.34
STAI-T → CASI	0.27*	0.27	0.21	0.33
AUDIT → CASI	0.12*	0.12	0.06	0.17
DUDIT → CASI	-0.05*	-0.05	-0.1	-0.01

Abbreviations: CTQ, childhood trauma; CASI, anxiety sensitivity; AUDIT, alcohol use; CES-DC, depression; DUDIT, drug use; STAI-T, trait anxiety.

* $p<0.05$.

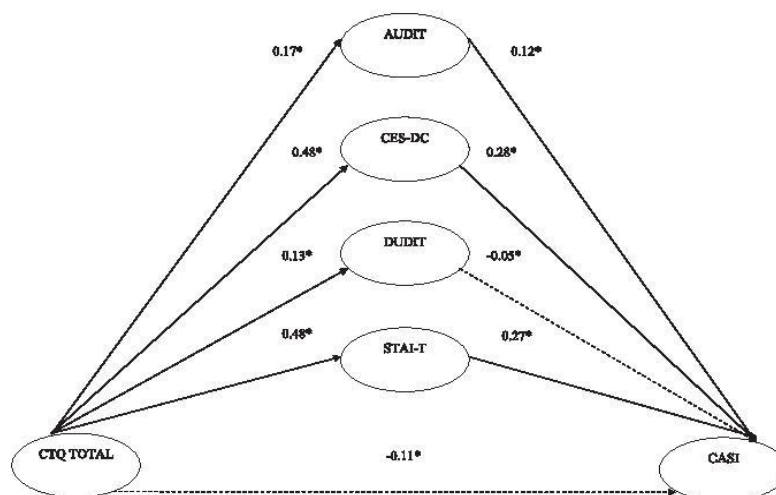


Fig. 1. Abbreviations: CTQ Total, Childhood Trauma Questionnaire total score; CASI, Child Anxiety Sensitivity Index; STAI-T, trait anxiety; DUDIT, drug use; CES-DC, self-reported depression; AUDIT, alcohol use.

Solid lines represent positive, significant path coefficients at $p<0.05$.

Dashed lines represent negative, significant path coefficients at $p<0.05$.

Table 3

Path coefficients: childhood trauma type, anxiety sensitivity and other risk factor variables.

Path	Path coefficient	Bootstrap mean	95% lower CI	95% upper CI	p-Value
Emotional abuse → CES-DC	0.4	0.4	0.33	0.46	Significant
Emotional abuse → STAI-T	0.33	0.33	0.26	0.39	Significant
Emotional abuse → DUDIT	0.14	0.14	0.06	0.22	Significant
Emotional abuse → AUDIT	0.11	0.11	0.02	0.19	Significant
Emotional abuse → CASI	0.05	0.05	−0.02	0.12	n.s.
Emotional neglect → STAI-T	0.24	0.24	0.18	0.31	Significant
Emotional neglect → CES-DC	0.1	0.1	0.04	0.16	Significant
Emotional neglect → CASI	−0.11	−0.11	−0.18	−0.04	Significant
Emotional neglect → AUDIT	0	0	−0.07	0.07	n.s.
Emotional neglect → DUDIT	−0.02	−0.01	−0.08	0.06	n.s.
Physical abuse → CES-DC	0.07	0.07	0	0.14	Significant
Physical abuse → DUDIT	0.1	0.1	0.01	0.2	Significant
Physical abuse → STAI-T	0.07	0.07	0	0.14	Significant
Physical abuse → AUDIT	0.05	0.05	−0.04	0.14	n.s.
Physical abuse → CASI	0	0	−0.07	0.07	n.s.
Sexual abuse → CES-DC	0.08	0.09	0.03	0.15	Significant
Sexual abuse → CASI	−0.06	−0.06	−0.11	−0.01	Significant
Sexual abuse → AUDIT	0.06	0.06	−0.02	0.14	n.s.
Sexual abuse → DUDIT	−0.03	−0.03	−0.1	0.05	n.s.
Sexual abuse → STAI-T	0	0	−0.06	0.06	n.s.
Physical neglect → AUDIT	0.02	0.02	−0.05	0.09	n.s.
Physical neglect → CASI	−0.03	−0.03	−0.09	0.03	n.s.
Physical neglect → CES-DC	0.02	0.02	−0.04	0.08	n.s.
Physical neglect → DUDIT	−0.03	−0.03	−0.11	0.04	n.s.
Physical neglect → STAI-T	0.02	0.03	−0.04	0.09	n.s.
STAI-T → CASI	0.27	0.27	0.2	0.34	Significant
AUDIT → CASI	0.11	0.11	0.06	0.17	Significant
CES-DC → CASI	0.25	0.25	0.18	0.32	Significant
DUDIT → CASI	−0.07	−0.07	−0.11	−0.02	Significant

Abbreviations: CES-DC, self-reported depression; STAI-T, trait anxiety; DUDIT, drug use; AUDIT, alcohol use; CASI, anxiety sensitivity; n.s., non-significant.

Table 4

Mediating effects of risk variables between CTQ trauma types and CASI.

CTQ trauma type	Risk variable	IE	z	p	Lower 95% CI	Upper 95% CI
Emotional abuse	AUDIT	0.03	3.55	< 0.01	0.02	0.06
	STAI-T	0.23	9.29	< 0.01	0.18	0.28
	CES-DC	0.27	9.69	< 0.01	0.21	0.32
Emotional neglect	STAI-T	0.21	9.75	< 0.01	0.16	0.26
	CES-DC	0.13	7.46	< 0.01	0.1	0.18
Physical abuse	STAI-T	0.2	8.99	< 0.01	0.16	0.25
	CES-DC	0.23	9.48	< 0.01	0.18	0.28
Sexual abuse	CES-DC	0.2	8.19	< 0.01	0.15	0.25

Abbreviations: CTQ, Childhood Trauma Questionnaire; CASI, anxiety sensitivity; AUDIT, alcohol use; STAI-T, trait anxiety; CES-DC, self-reported depression; IE, indirect effect.

AUDIT and the DUDIT, explained 21.36% of the variance in the CASI ($R^2=0.21$, $F(9, 1139)=34.38$, $p<0.01$). The following variables significantly predicted CASI scores: CTQ emotional neglect ($\beta=-0.11$, $t(1139)=-3.31$, $p<0.01$), STAI-T ($\beta=0.25$, $t(1139)=7.67$, $p<0.01$), CES-DC ($\beta=0.27$, $t(1139)=7.92$, $p<0.01$), and AUDIT ($\beta=0.11$, $t(1139)=3.91$, $p<0.01$). Examination of the redundancy table indicated no multicollinearity between the variables as the tolerance values were all above 0.2.

Results from the PLS mediator model indicated a number of significant, positive associations between certain CTQ trauma types and risk variables, and positive significant path coefficients were evident between all risk variables and the CASI, with the exception of the DUDIT (see Table 3). No positive significant direct effects were evident between any of the childhood trauma types and the CASI. Based on results from the PLS model, a number of potential mediating effects were analysed using Sobel's tests (see Table 4). In terms of emotional neglect and physical abuse, both trait anxiety

and depression had a mediating effect on AS. With regard to emotional abuse, trait anxiety, depression and alcohol use, despite the effect of alcohol use being small, had a mediating effect on AS. With regard to sexual abuse, depression was found to have a mediating effect. There were no positive, significant path coefficients evident between physical neglect and any of the risk factor variables or between physical neglect and the CASI.

3.6.5. Moderator effects: CTQ trauma types and protective variables

Results showed that the A-COPE had a moderating effect on the relationship between emotional abuse and the CASI ($\Delta R^2=-0.01$, $F_{\text{to remove}}=8.05$, $p<0.01$), indicating that in the context of low coping, the relationship between emotional abuse and anxiety sensitivity is strengthened, than if coping was high. In terms of resilience, CD-RISC scores had a moderating effect on the relationship between physical neglect and anxiety sensitivity ($\Delta R^2=-0.01$, $F_{\text{to remove}}=16.09$, $p<0.01$). Our results indicated that if resilience levels are low, there is a negative relationship between physical neglect and CASI scores, thus the higher the levels of physical neglect, the lower the anxiety sensitivity. However, if resilience levels are high, there is a fairly strong positive relationship between physical neglect and anxiety sensitivity with higher levels of physical neglect implying higher anxiety sensitivity. The CD-RISC also had a moderating effect on the relationship between emotional neglect and anxiety sensitivity ($\Delta R^2=-0.01$, $F_{\text{to remove}}=11.35$, $p<0.01$). This result indicates that if the CD-RISC is low, there is a negative relationship between emotional neglect and anxiety sensitivity, thus the greater the emotional neglect, the lower the anxiety sensitivity. However, if resilience levels are high, a strong positive relationship is evident between emotional neglect and anxiety sensitivity with greater emotional neglect implying higher anxiety sensitivity. That said, despite finding significant moderating effects for resilience, further investigation of the data showed a trend for a positive correlation in the

more extreme high resilience cases. This, however, pertains to a small subgroup of the data and could likely reflect random variation in the data.

4. Discussion

To the best of our knowledge, these findings provide the first data on the predictive potential of childhood trauma and childhood trauma types on AS; and the potential mediating and moderating roles of other risk (i.e. trait anxiety, depression, alcohol and drug use) and protective variables (i.e. resilience and coping), respectively, in primarily non-Caucasian, female, school-attending youth.

The average AS score in our sample was higher than that reported in a number of previous studies in children and adolescents (Ginsburg and Drake, 2002; Silverman et al., 1991; van Beek et al., 2005) and comparable with mean AS levels reported in African American school-attending children (Lambert et al., 2004) and pre-adolescents (Rabian et al., 1999). Rabian et al. (1999) suggested that AS may be influenced by race as they reported that significantly higher AS scores were evident in non-Caucasian children compared with Caucasian children.

Girls scored significantly higher than boys on AS (overall and by subscale scores, i.e. physical, social and psychological concerns), consistent with a number of studies in female children, adolescents and young adults (Ginsburg and Drake, 2002; Muris et al., 2001; Stewart et al., 1997). Gender differences in AS scores have been attributed to differences in gender role socialisation and orientation (Ginsburg and Drake, 2002), an under-reporting bias in males (Pierce and Kirkpatrick, 1992); genetic factors influencing AS dimensions in females (Taylor et al., 2008), and potential item bias (Van Dam et al., 2009). Our findings in terms of heightened levels of AS suggest that AS may be a specific risk factor in the development of anxiety disorders in black and mixed-race youth, and in girls in particular.

The average childhood trauma score in our sample was considerably higher than that reported in a comparable sample of predominantly mixed-race adolescents (Suliman et al., 2009). We found no significant gender differences in total childhood trauma or trauma type scores. In terms of trait anxiety, depression and alcohol and drug use, girls scored significantly higher than boys on trait anxiety and depression; and boys scored significantly higher than girls in terms of alcohol and drug use. Our findings are consistent with those studies that have found either elevated or significantly higher levels of trait anxiety (Mattis and Ollendick, 2002; Muris et al., 2001; Silverman et al., 1991) and depression (Mattis and Ollendick, 2002; Muris et al., 2001; Suliman et al., 2009) in female adolescents and young adults; and either elevated or significantly higher levels of substance use in males (Merikangas et al., 2010; Opland et al., 1995; Wu et al., 2010). Overall, high levels of self-reported depression, hazardous/harmful alcohol use and possible dependence and likely drug-related problems characterise this sample. No gender differences were evident in levels of resilience and coping orientation. Taken together, these findings suggest that girls are at greater risk than boys for early onset anxiety disorders as girls have significantly higher rates of trait anxiety and depression despite the same rates of childhood trauma, coping orientation and resilience as boys.

We found that depression, trait anxiety and alcohol use mediated the relationship between childhood trauma overall and AS and between certain childhood trauma types (i.e. emotional, physical and sexual abuse, emotional neglect) and AS. Of note, neither resilience nor coping orientation had any moderating effect on the relationship between childhood trauma overall and AS, however, coping orientation moderated the relationship between emotional abuse and AS, suggesting that in the context of

low levels of coping, a stronger relationship between emotional abuse and AS is evident, than if coping levels are high.

These results suggest that youth who experience high levels of childhood trauma (i.e. overall, or emotional, and/or physical and/or sexual abuse, and/or emotional neglect) are more likely to have high levels of trait anxiety, or depression or alcohol use and through high levels of trait anxiety, or depression or alcohol use, are more likely to be high on AS. Additionally, levels of resilience or coping do not appear to mitigate the effects of overall childhood trauma on AS, in our sample.

In line with our findings, previous research has shown that trait anxiety and AS are significantly and positively correlated (for example, Muris et al., 2001). Additionally, previous studies in child and adolescent samples have reported associations between trait anxiety and threat events (Eley and Stevenson, 2000) and have reported elevated or clinical levels of trait anxiety in adolescents diagnosed with panic attacks (Hoffman and Mattis, 2000) that are characterised by heightened levels of AS (Weems et al., 2002). Furthermore, significantly higher levels of trait anxiety have been documented in adults with depression or anxiety disorders and a history of childhood maltreatment in comparison with non-abused individuals with the same disorders (Handa et al., 2008). Self-reported depression has previously been found to be associated with childhood trauma (Suliman et al., 2009) and AS scores overall (Weems et al., 1997). In youth, alcohol and drug use problem severity have been reported to be associated with childhood trauma (Rosenkranz et al., 2012) and Stewart and Zeitlin (1995) reported that significantly more youth with high levels of AS consumed alcohol primarily for coping-related motives.

In sum, high levels of AS were evident in our sample and females scored significantly higher than males on AS overall and on each of the AS subscales. Females also had significantly higher trait anxiety and depression, while males had significantly higher alcohol and drug use problems. Our results suggest that in the context of childhood trauma, trait anxiety, self-reported depression and alcohol use play a significant role in heightened levels of AS and may be considered vulnerability factors that mediate subsequent heightened AS in adolescents and young adults with childhood trauma histories. Of note, neither childhood trauma overall nor any of the childhood trauma categories (i.e. sexual, emotional and physical abuse; and emotional and physical neglect), had significant positive direct effects on AS. Our findings underscore the influence of depression, trait anxiety and alcohol use in the context of childhood trauma as risk factors for the development of anxiety sensitivity and subsequent anxiety disorders in youth. Screening for depression, trait anxiety and alcohol use in youths with childhood trauma histories is recommended so as to identify those individuals most at risk for the development of anxiety-related disorders. Interventions aimed at targeting depressive symptomatology and high risk behaviours such as alcohol use in youths with maltreatment histories is recommended so as to decrease the likelihood of anxiety symptoms and disorders developing.

A number of study limitations deserve mentioning. Firstly, due to the cross-sectional nature of this study, inferences about causality cannot be made. Secondly, given that the study relied on self-report data and no diagnostic interviews were conducted to confirm levels of depression, alcohol and drug dependence, symptoms may have been over- or under-reported. Thirdly, due to the CTQ being a retrospective measure of childhood trauma with responses enquiring about events up to the age of 12 years in our study, responses may have been subject to recall bias. Despite these limitations, this study makes an important contribution to the growing body of literature on risk factors associated with the development of anxiety disorders in non-Western settings. It sheds light on possible protective factors that may mitigate the

effects of childhood trauma in non-Caucasian, predominantly female youths. The study identified high levels of AS in this representative sample of secondary school learners and documented significant gender differences in a number of risk factors associated with the development of anxiety disorders. Recommendations for further research include the replication of the study in samples in which ethnic groups are of comparable sizes and in which gender is relatively evenly spread. This will help determine whether the risk and protective factors investigated here have the same effects in more comparable samples of youth.

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Conflict of interest

The authors declare no conflict of interest.

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APPENDIX A3:

Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African sample



Anxiety Sensitivity in School Attending Youth: Exploratory and Confirmatory Factor Analysis of the 18-Item CASI in a Multicultural South African Sample

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Anxiety sensitivity (AS) is a risk factor for the development of anxiety disorders in youth. To date, the applicability of the Childhood Anxiety Sensitivity Index (CASI) in youth from a low or middle income country (LMIC) setting on the African continent has not been assessed. A representative sample of 1149 secondary school learners from 29 schools in Cape Town, South Africa, participated in the study. Participants completed the CASI on a single occasion. One-, two-, and four-factor models of the CASI were assessed. A one-factor solution that comprised items predominantly represented by physical concerns appeared to provide the best fit to our data, however, relatively low variance (26%) was explained. Subsequent item deletion resulted in a 9-item 'physical concerns' factor that showed good construct reliability (0.83) but also explained a low amount of variance (35%). In terms of gender, a one-factor model provided the best fit, however, low variance was explained (i.e., 25%). Configural, metric and scalar invariance of the CASI by gender was determined. Our results suggest that the 18-item CASI is not applicable to our target population and may require adaptation in this population; however, replication of this study in other multicultural adolescent samples in South Africa is first needed to further assess the validity of the AS construct as measured by the CASI.

Keywords: Childhood Anxiety Sensitivity Index (CASI), exploratory factor analysis, confirmatory factor analysis, gender, adolescents, South Africa

INTRODUCTION

Anxiety sensitivity (AS) is an established temperamental trait and vulnerability factor associated with fearfulness and anxiety pathology in both adults and youth (Reiss et al., 1986; McLaughlin et al., 2007; Naragon-Gainey, 2010; Viana and Gratz, 2012; Olthuis et al., 2014). AS is defined as the fear of anxiety-related bodily sensations and symptoms (e.g., feeling nervous, dizzy or shaky; heart beating fast; stomach growling) based on the belief that these somatic sensations have negative or even catastrophic physical, psychological or social consequences (e.g., being physically ill; psychological incapacitation; social embarrassment) (Reiss and McNally, 1985; Reiss, 1991). These beliefs or expectations are thought to increase an individual's pre-existing anxiety (Reiss, 1991).

In children and adolescents, AS has been shown to be strongly and significantly associated with measures of anxiety symptoms and anxiety disorder subtypes (McLaughlin et al., 2007; Essau et al., 2010), including panic attack symptomatology and distress levels due to panic symptomatology (Lau et al., 1996). Furthermore, AS has been shown to prospectively predict the development of anxiety symptoms in children, adolescents (Schmidt et al., 2010) and young adults (Schmidt et al., 2008), including the incidence of spontaneous panic attacks (in those without panic histories) and overall Axis I diagnoses, in non-clinical young adults (Schmidt et al., 2006). It has been established that individuals diagnosed with anxiety disorders report significantly greater levels of AS than non-clinical controls (Olatunji and Wolitzky-Taylor, 2009), signifying that heightened AS is a risk factor for anxiety symptoms and disorders.

In adults, AS is commonly measured using the Anxiety Sensitivity Index (ASI; Peterson and Reiss, 1987), a 16-item, self-report questionnaire rated on a 5-point scale ranging from 0 to 4 ('very little' to 'very much'). The 18-item Childhood Anxiety Sensitivity Index (CASI; Silverman et al., 1991), typically used to measure AS in children and adolescents, was derived from the ASI items but was modified to be age-appropriate, relevant and readily understandable to children (Silverman et al., 1991). Responses on the CASI are rated on a 3-point scale ranging from 1 to 3 ('none' to 'a lot').

Results from early factor analytic studies on AS in adult samples (e.g., spider phobic college students, adult psychiatric outpatients and college students), as measured by the ASI, suggested that the ASI is unifactorial in nature and thus consists of a single factor (Reiss et al., 1986; Taylor et al., 1991). Comparable findings were documented in Spanish treatment seekers (Sandin et al., 1996) and in Native Americans (Norton et al., 2004). More recently, a meta-analysis of AS indicated that AS in adults is multidimensional, consisting of three distinct, yet intercorrelated factors (Olatunji and Wolitzky-Taylor, 2009) that are hierarchically arranged and load on a single higher-order factor (Zinbarg et al., 1997). The three lower-order factors comprise (1) fear of physical symptoms, (2) fear of publicly observable anxiety symptoms and (3) fear of cognitive dyscontrol (Olatunji and Wolitzky-Taylor, 2009). That said, some studies have found that the ASI is comprised of two (e.g., Schmidt and Joiner, 2002) or even four (e.g., Carter et al., 1999) underlying factors.

Results from studies that have explored the factor structure of the CASI in children and adolescents appear relatively inconsistent. In one of the first of such studies, using the 18-item CASI in a sample of clinical and non-clinical children and pre-adolescents, Silverman et al. (1999) found support for a hierarchical multidimensional model in which three or four-factors were present, of which two were robust, namely, physical and mental incapacitation concerns. Subsequent confirmatory factor analysis by Silverman et al. (2003), in samples of non-clinical children and adolescents, based on results from past factor analytic studies, supported a hierarchical factor model for AS, due to a strong general factor. Furthermore, there was evidence for four lower-order factors (i.e., disease concerns, unsteady concerns, mental incapacitation concerns, and social

concerns) that fit the data well (Silverman et al., 2003). That said, a three-factor solution, as found in the adult literature, has also commonly been documented in non-clinical samples of children and adolescents using the CASI (van Widenfelt et al., 2002; McLaughlin et al., 2007). Given the aforesaid, the factor structure of the CASI is still essentially questionable and may potentially vary according to sample characteristics.

In terms of gender, a number of studies that have compared CASI factor models across gender have shown that AS appears similar in structure for males and females. For example, Walsh et al. (2004) reported similar structures across gender for their three-factor lower-order models in a large school-attending sample of children and adolescents. Similarly, Wright et al. (2010) found that the fit for a three-factor model was similar across gender in a comparable sample and Silverman et al. (2003) found support for factorial invariance across gender for their four-factor lower-order models in both clinical and non-clinical samples of children and adolescents.

An important finding, when examining the AS construct in youth from non-Caucasian ethnic groups, is that AS appears to manifest in ways different to that commonly found in Caucasian samples of children, adolescents and young adults (Carter et al., 1999; Lambert et al., 2004). For example, Lambert et al. (2004) reported higher mean AS scores in their sample of 144 African American fourth- and fifth-grade students, than is commonly found in studies of non-clinical Caucasian children and adolescents. Furthermore, they found that the three- and four-factor higher-order model as proposed by Silverman et al. (1999) did not provide a good fit, but rather that a two-factor model best fit their data. The two-factors were 'physical concerns' and 'mental incapacitation,' with little support for a social concerns or control factor. In addition, contrary to the general trend in Caucasian samples, they found no gender difference in levels of AS in their sample. Similarly, Carter et al. (1999), using the ASI in a sample of 221 African American college students, found that the commonly agreed upon three factor model by Zinbarg et al. (1997) of 'physical concerns,' 'mental incapacitation concerns,' and 'social concerns,' did not provide a good fit to their data. Rather, they found support for a four-factor model, with the composition of factors seemingly different from that commonly found among Caucasian samples (Carter et al., 1999). Lambert et al. (2004) indicated that different factor structures may reflect cross-ethnic dissimilarities in the AS construct.

To date, the applicability of the CASI, a measure developed in the United States, has not been assessed in South African youth. As such, the current study examined the construct of AS in a representative sample of predominantly Black and mixed-race secondary school learners from Cape Town, South Africa. The primary aim of the study was to assess the factorial validity of the CASI by firstly, conducting an exploratory factor analysis (EFA) to determine the underlying factor structure of the CASI in our sample overall and by gender and secondly, by performing confirmatory factor analyses (CFA) on the sample overall and by gender to examine the fit of the models that emerged from the EFA. An investigation into the factorial validity of the CASI will aid our understanding of the etiology of AS

in a representative sample of predominantly non-Caucasian secondary school attenders, in a lower-income, multi-cultural setting.

MATERIALS AND METHODS

Participants and Procedure

Permission to access secondary schools in Cape Town and to conduct the study was provided by the Western Cape Education Department (WCED) and the Health Research Ethics Committee at Stellenbosch University, respectively.

The education districts of Cape Town, as indicated by the WCED, were stratified according to those representing urban education districts (i.e., Metro North, Metro South, Metro East, and Metro Central). Schools ($n = 29$) were then randomly sampled from each of these districts to obtain a sample representative of urban public secondary schools in Cape Town. Schools identified, as described above, were approached to participate in the study and those that agreed to participate were requested to provide the names of all learners from grades 8 to 12. Thereafter, a sample of 20 learners per grade, per school, was randomly selected so as to ensure a representative sample of secondary school learners from Cape Town. Written informed consent was obtained from parents or guardians and written assent was obtained from the learners themselves. Study questionnaires were completed at the schools on a single occasion.

The resulting sample of learners comprised 1149 youths aged between 13 and 23 years ($M = 16.24$, $SD = 1.95$). The majority of the sample was classified as adolescents aged from 13 to 18 years (995/1149, 86.6%). The mean level of education was grade 9 and ranged between grades 8 and 12. Over half the sample consisted of girls (689/1149, 59.97%). The vast majority of the sample identified themselves as black (68.9%), followed by mixed-race (27.7%).

Measure

The CASI (Silverman et al., 1991) is an 18-item self-report questionnaire designed for use with school-age children and adolescents. The CASI measures the fear of anxiety symptoms on a 3-point Likert-type scale by asking participants to rate the extent to which they believe the experience of anxiety will result in negative consequences, comprising physical, psychological and social concerns. The CASI yields a total score by summing the 18 items and has a range of 18–54 with higher scores reflecting higher levels of AS. Silverman et al. (1991) reported adequate internal consistency and reliability for the CASI in their sample of clinical and non-clinical, primarily Caucasian, children and adolescents. In the current study, for the total sample, the CASI had good internal consistency ($\alpha = 0.81$), with Cronbach's alphas of 0.80 and 0.81 for boys and girls, respectively. Corrected item-total correlation values ranged from 0.207 to 0.509. Three of eighteen items (i.e., items 1, 5, and 17) (see **Table 1**) displayed values that were below the commonly accepted level of 0.3 (Pallant, 2007). However, examination of the item-total statistics (i.e., Cronbach's alpha if item deleted) indicated that removal of

any item would not have improved the reliability of the CASI and thus all 18 CASI items were retained.

Statistical Analyses

A very small amount of missing data was observed in the CASI items due to the strict procedures followed during the data collection phase, with all data being collected at schools and subsequently all study questionnaires being examined for missing data at the respective schools, at the time of questionnaire completion. As such, a maximum of 1.22% of missing values was evident in the CASI items. Missing data were replaced by means of the k-nearest neighbor imputation method.

Descriptive statistics were computed for demographic data, with variables of interest including age, gender, and ethnicity. Frequencies of responses to the 18 CASI items were reported, along with item means (and SD's), skewness and kurtosis. Differential item functioning (DIF) analyses, using the lordif package (Choi et al., 2011), was conducted using iterative hybrid ordinal logistic regression (IRT DIF) to determine whether males and females were consistent in how they interpreted and endorsed CASI items.

Examination of the underlying factor structure of the CASI for the total sample and by gender was determined by means of EFA using principal components analysis (PCA) with oblique rotation. In addition to conducting Pearson correlations, polychoric correlations were calculated and it was determined that results were similar to those found for Pearson correlations. Factors retained were based on results of (1) parallel analysis, (2) Cattell's scree test and (3) a Kaiser's eigenvalue greater than one. A cut-off of 0.3, in conjunction with clinical judgment, was used as a reference to indicate salient item loadings. Thereafter, CFA, using Lisrel version 8.8, was conducted to test the suitability of the models that emerged from the EFA. Robust maximum-likelihood (RML) was used as the method of estimation; a useful estimation method employed to deal with possible non-normal data. All variables were treated as continuous variables. Multiple fit indices were used to indicate how well the proposed models fitted the data. The following indices were used in the present study: (1) the Root Mean Square Error of Approximation (RMSEA; should be 0.05 or lower); (2) the Standardized Root Mean Square Residual (SRMR; should be 0.08 or less); (3) the Comparative Fit Index (CFI; should be closer to 1); (4) the Goodness of Fit Index (GFI; should be 0.90 or higher); and (5) the Adjusted Goodness of Fit Index (AGFI; should be 0.90 or higher). To assist with model comparison and selection for analysis on the total sample, we reported the following information criteria: (1) the Akaike Information Criterion (AIC; lower values are preferred) and (2) the Consistent Akaike Information Criterion (CAIC, lower values are preferred). Structural equation modeling provided an indication of the strength of the relationship between CASI items and proposed factors and between individual factors in each model. As such, the total sample of 1149 participants was randomly split into two. The first cohort, on which the EFA was conducted, consisted of 30% of the sample (345/1149) and the second cohort, on which CFA was run, consisted of the remaining 70% (804/1149). Similarly, EFA was conducted on 30% of males and females and CFA was conducted on the remaining

70% of males and females, using the above named procedures. Finally, we examined measurement invariance of the CASI across genders, using multigroup CFA with RML estimation, to assess configural (i.e., whether the same model structure holds across genders) and metric (i.e., whether factor loadings are similar across genders) invariance. In terms of assessing scalar invariance (i.e., whether intercepts are equal across genders), maximum likelihood estimation was employed.

RESULTS

Descriptive Statistics: 18-Item CASI

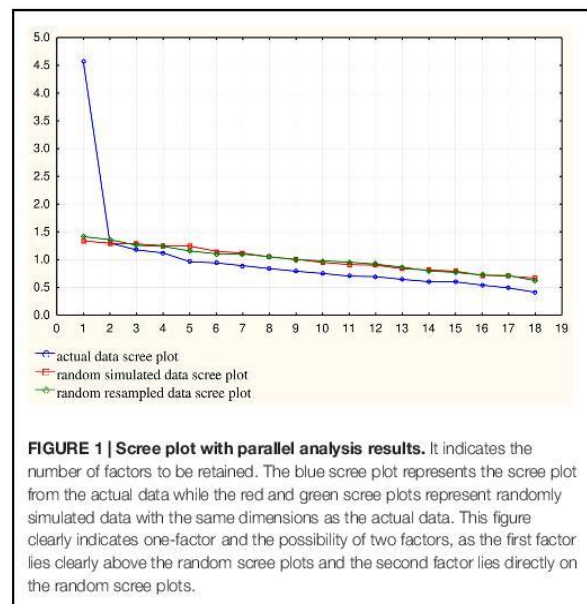
The frequencies of responses to the individual CASI items as well as the item means, skewness and kurtosis values are presented in **Table 1**.

DIF by Gender

Results indicated that 2 of the 18 items had DIF, namely, items 1 and 3 [i.e., 'I don't want other people to know when I feel afraid' ($p = 0.023$) and 'It scares me when I feel shaky' ($p = 0.001$)]. The magnitude of DIF was calculated for the two items and was found to be negligible (Nagelkerke $R^2 < 0.035$).

EFA of the CASI for the Total Sample

Factors retained were based on results of the parallel analysis, Cattell's scree test and a Kaiser's eigenvalue greater than one. Parallel analysis indicated a one-factor model or the possibility of a two-factor model, whereas the scree plot indicated a two-factor model. Using an eigenvalue greater than one rule, four-factors were suggested. As



such, we explored one-, two-, and four-factor models. See **Figure 1** depicting the scree plot and results of the parallel analysis.

One-Factor Model

The one-factor in the model explained 25.35% of the variance. Loadings were relatively low, all below 0.65. All items with loadings above 0.5 were related to physical concerns (see **Table 2**).

TABLE 1 | 18-item CASI: corrected item-total correlation values (CITC), item response frequencies, mean, skewness and kurtosis.

CASI items	CITC	Item responses [n(%)]			Mean (SD)	Skewness	Kurtosis
		None	Some	A lot			
Item 1	0.207	262 (23)	718 (62)	169 (15)	1.92 (0.61)	0.041	-0.320
Item 2	0.365	501 (44)	432 (38)	216 (19)	1.75 (0.75)	0.441	-1.113
Item 3	0.502	415 (36)	452 (39)	282 (25)	1.88 (0.77)	0.201	-1.292
Item 4	0.436	404 (35)	378 (33)	367 (32)	1.97 (0.82)	0.059	-1.506
Item 5	0.227	139 (12)	321 (28)	689 (60)	2.48 (0.70)	-0.979	-0.358
Item 6	0.470	249 (22)	493 (43)	407 (35)	2.14 (0.74)	-0.227	-1.165
Item 7	0.340	362 (32)	450 (39)	337 (29)	1.98 (0.78)	0.038	-1.355
Item 8	0.405	418 (36)	478 (42)	253 (22)	1.86 (0.75)	0.242	-1.196
Item 9	0.509	335 (29)	428 (37)	386 (34)	2.04 (0.79)	-0.079	-1.398
Item 10	0.466	279 (24)	402 (35)	468 (41)	2.16 (0.79)	-0.300	-1.339
Item 11	0.391	299 (26)	542 (47)	308 (27)	2.01 (0.73)	-0.012	-1.106
Item 12	0.422	214 (19)	403 (35)	532 (46)	2.28 (0.76)	-0.508	-1.098
Item 13	0.303	586 (51)	428 (37)	135 (12)	1.61 (0.69)	0.693	-0.677
Item 14	0.509	353 (31)	472 (41)	324 (28)	1.97 (0.77)	0.043	-1.300
Item 15	0.380	703 (61)	326 (28)	120 (10)	1.49 (0.68)	1.036	-0.174
Item 16	0.402	323 (28)	564 (49)	262 (23)	1.95 (0.71)	0.077	-1.024
Item 17	0.240	242 (21)	518 (45)	389 (34)	2.13 (0.73)	0.203	-1.109
Item 18	0.472	402 (35)	450 (39)	297 (26)	1.91 (0.77)	0.159	-1.319

Standard Error of Skewness = 0.072; Standard Error of Kurtosis = 0.144.

TABLE 2 | EFA one-factor model.

Item	Description of CASI items	Loading
1	Don't want other people to know when I am afraid.	0.42
2	When I can't keep mind on schoolwork, worry I going crazy.	0.42
3	Scares me when I feel shaky.	0.64
4	Scares me when I feel like I am going to faint.	0.55
5	Important for me to stay in control of my feelings.	0.28
6	Scares me when my heart beats fast.	0.57
7	Embarrasses me when my stomach growls.	0.49
8	Scares me when feels like going to throw up.	0.49
9	When my heart beats fast, worry something wrong with me.	0.62
10	Scares me when having trouble getting my breath.	0.55
11	When my stomach hurts, worry that I might be really sick.	0.51
12	Scares me when can't keep my mind on schoolwork.	0.48
13	Other kids can tell when I feel shaky.	0.47
14	Unusual feelings in my body scare me.	0.59
15	When I am afraid, worry that I might be crazy.	0.47
16	Scares me when I feel nervous.	0.49
17	Don't like to let my feelings show.	0.27
18	Funny feelings in my body scare me.	0.58

Two-Factor Model

Combined, the two-factors in the model explained 32.57% of the total variance, with the first and second factors accounting for 25.35% (eigenvalue = 4.56) and 7.22% (eigenvalue = 1.3) of the variance, respectively. The first factor (items 9, 11, 3, 2, 13, 15, 6, 18, 7, 8, 10, 16, 14, and 12) was labeled 'physical and psychological concerns' and consisted of a combination of items representing both physical and psychological concerns (see **Table 3**). The second factor was labeled 'social and control concerns' and consisted predominantly of items representing social concerns

(i.e., items 1, 5, and 17). Item 4 ('It scares me when I feel like I am going to faint'), which loaded onto the second factor, represented an item also commonly associated with factors labeled in the literature as an 'unsteady concern' (Silverman et al., 2003), a 'control concern' (Silverman et al., 1999) and a 'physical concern' (Silverman et al., 2003). The correlation between the two-factors was 0.30.

Four-Factor Model

The four-factor model, indicated by eigenvalues greater than 1, explained 45.31% of the total variance. The first factor accounted for 25.35% (eigenvalue = 4.56) of the variance; the second factor explained 7.22% (eigenvalue = 1.30) and the third and fourth factors explained 6.52% (eigenvalue = 1.17) and 6.22% (eigenvalue = 1.12) of the variance, respectively. The first factor was labeled 'mental incapacitation and physical concerns' (items 15, 16, 18, and 9) (see **Table 4**). The second factor was labeled 'social concerns' (items 17 and 1), and the third factor and fourth factors were labeled 'control concerns' (items 5, 12, and 2) and 'physical concerns' (items 10, 8, 14, 7, 11, 4, 13, 6, and 3), respectively. Correlations between the four-factors were relatively modest and ranged from 0.05 to 0.37.

CFA of the CASI for the Total Sample

Confirmatory factor analyses was conducted to assess the model fit for two- and four-factor models as well as a one-factor model. See **Table 5** for fit indices for these models. Results indicated acceptable goodness of fit indices for the three models, particularly the one- and four-factor models. Similarly, AIC and CAIC values suggested that the one- and four-factor models were more suitable than the two-factor model and as such, we report further on the one- and four-factor CFA models.

TABLE 3 | EFA two-factor model.

Item	Description of CASI items	Factor 1	Factor 2
9	When my heart beats fast, worry something wrong with me.	0.69	
11	When my stomach hurts, worry that I might be really sick.	0.62	
3	Scares me when I feel shaky.	0.60	
2	When I can't keep mind on schoolwork, worry I going crazy.	0.57	
13	Other kids can tell when I feel shaky.	0.56	
15	When I am afraid, worry that I might be crazy.	0.55	
6	Scares me when my heart beats fast.	0.54	
18	Funny feelings in my body scare me.	0.48	
7	Embarrasses me when my stomach growls.	0.46	
8	Scares me when feels like going to throw up.	0.43	
10	Scares me when having trouble getting my breath.	0.42	
16	Scares me when I feel nervous.	0.40	
14	Unusual feelings in my body scare me.	0.39	
12	Scares me when can't keep my mind on schoolwork.	0.38	
17	Don't like to let my feelings show.		0.74
1	Don't want other people to know when I feel afraid.		0.64
5	Important for me to stay in control of my feelings.		0.41
4	Scares me when I feel like I am going to faint.		0.38

Factor 1: physical and psychological concerns; Factor 2: social and control concerns.

TABLE 4 | EFA four-factor model.

Item	Description of CASI items	Factor 1	Factor 2	Factor 3	Factor 4
15	When I am afraid, worry that I might be crazy.	0.76			
16	Scares me when I feel nervous.	0.50			
18	Funny feelings in my body scare me.	0.50			
9	When my heart beats fast, worry something wrong with me.	0.48			
17	Don't like to let my feelings show.		0.74		
1	Don't want other people to know when I feel afraid.		0.63		
5	Important for me to stay in control of my feelings.			0.74	
12	Scares me when can't keep my mind on schoolwork.			0.65	
2	When I can't keep mind on schoolwork, worry I going crazy.			0.52	
10	Scares me when having trouble getting my breath.				0.78
8	Scares me when feels like going to throw up.				0.62
14	Unusual feelings in my body scare me.				0.62
7	Embarrasses me when my stomach growls.				0.45
11	When my stomach hurts, worry that I might be really sick.				0.43
4	Scares me when I feel like I am going to faint.				0.42
13	Other kids can tell when I feel shaky.				0.40
6	Scares me when my heart beats fast.				0.39
3	Scares me when I feel shaky.				0.36

Factor 1: mental incapacitation and physical concerns; Factor 2: social concerns; Factor 3: control concerns; Factor 4: physical concerns.

TABLE 5 | Fit indices and information criteria for the one-, two- and four-factor models.

	One factor	Two factors	Four Factors
$\chi^2(df)$	381.38(135)*	403.76(134)*	342.41(129)*
RMSEA	0.048	0.05	0.045
SRMR	0.056	0.044	0.053
CFI	0.97	0.95	0.97
GFI	0.98	0.95	0.98
AGFI	0.97	0.93	0.97
AIC	453.37	477.76	426.41
CAIC	658.20	688.27	665.37

χ^2 , Satorra-Bentler Weighted Least Squares Chi-Square; df, Degrees of Freedom; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized Root Mean Square Residual; CFI, Comparative Fit Index; GFI, Goodness of Fit Index; AGFI, Adjusted Goodness of Fit Index; AIC, Akaike Information Criterion; CAIC, Consistent Akaike Information Criterion; * $p < 0.001$.

Construct Reliability and Variance Extracted

With regard to the one-factor model, good construct reliability was evident (i.e., $\alpha = 0.85$). That said, the variance extracted was relatively low (i.e., 26%). Examination of the item loadings between the CASI items and the individual factor showed that 11 of the 18 items were 0.5 and above and the remaining 7 were lower than 0.5 (see Table 6), with all loadings being significant (i.e., t -statistic > 1.96). The majority of items with higher loadings were representative of items that were related to 'physical concerns.' Given these results, a one-factor model appears to provide the best fit, as previously suggested by the scree plot.

In terms of the four-factor model, the Lisrel software flagged a 'positive definite' warning, indicating highly correlated factors and thus suggesting that less than four factors are evident.

Deletion of Items from the One-Factor CFA Model

The one-factor CFA model was re-examined in order to identify items for possible deletion in order to determine a subset of items suggestive of a definite underlying construct. The inclusion and exclusion of items was based on both the examination of item loadings and discriminating between items that made clinical sense to include and exclude. As the majority of items with high loadings were those that related to 'physical concerns,' and thus suggested that a 'physical concerns' scale was dominant, we included all 'physical concerns' items and excluded those items that related to 'psychological,' 'social' and 'control concerns.' The resulting 'physical concerns' scale included the following nine items: (1) item 3 ('scares me when I feel shaky'), (2) item 4 ('scares me when I feel like I am going to faint'), (3) item 6 ('scares me when my heart beats fast'), (4) item 8 ('scares me when feels like going to throw up'), (5) item 9 ('when my heart beats fast, worry something wrong with me'), (6) item 10 ('scares me when having trouble getting my breath'), (7) item 11 ('when my stomach hurts, worry that I might be really sick'), (8) item 14 ('unusual feelings in my body scare me') and (9) item 18 ('funny feelings in my body scare me').

Subsequently, both EFA and CFA, using the above-mentioned nine items, were conducted on the test data. The EFA clearly indicated the presence of one-factor and the amount of variance explained was 35.48%, with item loadings ranging from 0.51 to 0.66. The subsequent CFA indicated that the model explained 35% of the variance and the construct reliability was 0.83. Item loadings ranged from 0.48 to 0.67. The following fit indices were determined: $\chi^2(df) = 101.09(27)$, $p < 0.001$; RMSEA: 0.058; SRMR: 0.048; CFI: 0.98; GFI: 0.99; and AGFI: 0.98. These results

TABLE 6 | Item loadings between CASI items and individual CASI factor from the one-factor CFA model.

Item	Description of CASI items	Item loading
1	<i>Don't want other people to know when I am afraid.</i>	0.16
2	<i>When I can't keep mind on schoolwork, worry I going crazy.</i>	0.49
3	Scares me when I feel shaky.	0.60
4	Scares me when I feel like I am going to faint.	0.54
5	<i>Important for me to stay in control of my feelings.</i>	0.28
6	Scares me when my heart beats fast.	0.62
7	<i>Embarrasses me when my stomach growls.</i>	0.38
8	Scares me when feels like going to throw up.	0.51
9	When my heart beats fast, worry something wrong with me.	0.66
10	Scares me when having trouble getting my breath.	0.59
11	<i>When my stomach hurts, worry that I might be really sick.</i>	0.48
12	Scares me when can't keep my mind on schoolwork	0.56
13	<i>Other kids can tell when I feel shaky.</i>	0.36
14	Unusual feelings in my body scare me.	0.64
15	When I am afraid, worry that I might be crazy.	0.53
16	Scares me when I feel nervous.	0.50
17	<i>Don't like to let my feelings show.</i>	0.29
18	Funny feelings in my body scare me.	0.59

Items in italics reflect those with path coefficients lower than 0.5.

indicate good fit indices for the 9-item one-factor CFA model; however, the variance explained by this one-factor model remained low. The 9-item scale had good internal consistency ($\alpha = 0.77$).

EFA and CFA of the CASI by Gender

For both males and females, parallel analysis and scree plot results indicated that a one-factor model was most suitable. The one-factor in the model explained 25.38% and 24.40% of the variance for males and females, respectively. Factor loadings ranged between 0.16 and 0.67 for males and between 0.31 and 0.61 for females (see Table 7).

In terms of CFA by gender, the fit indices for the one-factor model for both males and females (see Table 8), were acceptable. With regard to the one-factor model, good construct reliability was evident for both males and females (i.e., 0.85). As with the one-factor CFA model for the total sample, the variance extracted by the one-factor CFA model by gender was relatively low (i.e., 25% for both males and females). Item loadings between the CASI items and the individual factor for the one-factor CFA model by gender ranged from 0.23 to 0.67 for males and from 0.15 to 0.64 for

TABLE 7 | One-factor EFA and CFA: item loadings by gender.

CASI items	EFA item loadings		CFA item loadings	
	Males	Females	Males	Females
1	0.48	0.35	0.23	0.15
2	0.31	0.47	0.51	0.46
3	0.67	0.60	0.62	0.57
4	0.51	0.57	0.58	0.49
5	0.25	0.31	0.29	0.29
6	0.63	0.50	0.61	0.60
7	0.53	0.45	0.44	0.31
8	0.52	0.46	0.47	0.54
9	0.67	0.57	0.67	0.64
10	0.51	0.55	0.56	0.60
11	0.55	0.46	0.44	0.50
12	0.46	0.47	0.54	0.54
13	0.53	0.45	0.34	0.38
14	0.57	0.60	0.64	0.64
15	0.44	0.50	0.49	0.54
16	0.48	0.49	0.48	0.52
17	0.16	0.33	0.27	0.29
18	0.51	0.61	0.54	0.60

TABLE 8 | Fit indices for the one-factor EFA model by gender.

	Males	Females
χ^2 (df) p	381.38(135)*	403.76(134)*
RMSEA	0.048	0.050
SRMR	0.056	0.044
CFI	0.97	0.95
GFI	0.98	0.95
AGFI	0.97	0.93

χ^2 , Satorra-Bentler Weighted Least Squares Chi-Square; df, Degrees of Freedom; RMSEA, Root Mean Square Error of Approximation; SRMR, Standardized Root Mean Square Residual; CFI, Comparative Fit Index; GFI, Goodness of Fit Index; AGFI, Adjusted Goodness of fit Index; * $p < 0.001$.

females (see Table 7), with all loadings being significant (i.e., t -statistic > 1.96).

Measurement Invariance by Gender

Configural invariance of the CASI was tested by examining whether an unconstrained model (i.e., outer loadings estimated separately for males and females) provided an acceptable fit. The configural invariance model indicated a reasonable fit, as evidenced by the RMSEA (0.047), the p -value for test of close fit (0.75) and the GFI (0.96). Further, we tested the metric invariance of the CASI by assessing if factor loadings were similar across genders. The p -value for differences between the constrained (i.e., model fitted under the hypothesis of equal outer loadings between males and females) and unconstrained models was 0.11. Scalar invariance of the CASI was tested by comparing a constrained model (i.e., under the hypothesis of equal intercepts) with an unconstrained model (i.e., intercepts estimated separately). Results indicated no differences between the models ($p = 0.32$). Taken together, these results provide

support for configural, metric and scalar invariance across genders.

DISCUSSION

As the CASI, a measure developed in the United States, has not been assessed in South African youth, the current study examined the construct of AS, as measured by the 18-item CASI, in a representative sample of predominantly Black and mixed-race secondary school learners in South Africa. We aimed to assess the factorial validity of the CASI by conducting EFA and subsequent CFA to assess the resulting models in our sample overall and by gender.

Exploratory factor analysis indicated that the CASI consisted of one, two, or four underlying factors. Subsequent results from the CFA suggested that, of the models, the one-factor solution provided the best fit to our data. High correlations between the latent variables in the four-factor CFA model were evident as a 'positive-definite' warning was flagged by the Lisrel software indicating that less than four-factors are evident. Despite our one-factor CFA model demonstrating good construct reliability (i.e., 0.85), it explained a relatively small amount of variance (26%). Furthermore, a number of the items (i.e., 7 of 18) had relatively low item loadings. These comprised items 1, 2, 5, 7, 11, 13, and 17. Items 2 and 11, however, had relatively higher item loadings that were just below 0.5 (i.e., 0.49 and 0.48, respectively). Items 1, 5, 7, 13, and 17 are items generally associated with social and control concerns (Silverman et al., 1999, 2003; Muris et al., 2001), with item 2 reflecting a psychological concern and item 11 reflecting a physical concern (Silverman et al., 1999, 2003). The remaining 11 items reveal concerns predominantly relating to physical concerns (or disease concerns) and also contain some items that reflect psychological concerns (or mental incapacitation concerns) [e.g., items 12 and 15]. Given that the one-factor model appeared to best fit our data, our findings indicate a lack of equivalence with models found in Western samples (Silverman et al., 1999, 2003; Muris et al., 2001; Lambert et al., 2004; Walsh et al., 2004).

In order to determine a subset of items suggestive of a definite underlying construct, a number of items from the one-factor CFA model were deleted and subsequent EFA and CFA analyses was conducted. Based on both high item loadings and clinical judgment, a 9-item 'physical concerns' factor was derived. The higher item loadings of the majority of 'physical concerns' items in the one-factor model suggest that the participants in this study may have better understood these items and thus answered them more accurately. That said, as with the 18-item one-factor CFA model, the 9-item model showed good internal consistency but the variance extracted remained low (i.e., 35%). There is agreement that the items that we included in our 9-item physical concerns measure is inclusive of all items previously found to be labeled as 'physical concerns' in previous factor analytic studies of AS (Silverman et al., 2003). Previous factor analytic studies have consistently revealed support for a robust 'physical concerns' factor, associated with the strongest item loadings (e.g., Silverman

et al., 1999; Chorpita and Daleiden, 2000). In a sample of adults with anxiety disorders, Zinbarg et al. (2001) found that their 'physical concerns' subscale (vs. 'social concerns' and 'mental incapacitation' subscales) of the 16-item ASI (1) had the largest correlation to fear responses in two physiological challenges (i.e., hyperventilation and carbon monoxide) and (2) uniquely contributed to variance in fear ratings during these challenges whilst the other two subscales did not, suggesting that the 'physical concerns' subscale plays a key role in panic disorder (Zinbarg et al., 2001). Of note, the items that constitute the 'physical concerns' factor previously mentioned (i.e., Zinbarg et al., 2001), duplicate those included in our 9-item measure. The 'physical concerns' factor [based on the three-factor model of Zinbarg et al. (1997)], assessed in adolescents and young adults (Dehon et al., 2005), displayed the largest partial correlation with anxiety (i.e., controlling for depression), compared with the 'social' and 'psychological concerns' factors, and it would be useful to determine whether our 9-item 'physical concerns' measure reveals similar findings, within the South African context, in future studies in samples comparable to the current study.

In terms of gender, we found that a one-factor model was suited to both males and females, however, in line with our results of the EFA and CFA for the total sample, the one-factor CFA model applied to both genders demonstrated good construct reliability (i.e., 0.85) but explained a relatively low amount of variance (25%). Our results showed support for configural, metric and scalar invariance across gender, indicating that the CASI assesses the same construct in both males and females in our sample.

Overall, a low amount of variance was extracted by the constructs from the individual CFA models in the sample overall and by gender. A relatively high level of item difficulty and complexity (e.g., the content of the questions and how they are phrased), resulting in the possible misinterpretation of the CASI items, may have influenced participants' responses on the CASI and may have thus contributed to our findings (i.e., relatively low factor loadings and low variance extracted). In sum, given our results, the applicability of both the 18-item CASI as well as the 9-item factor derived from the original measure has proven limited in the current sample. The 9-item 'physical concerns' factor derived from the 18-item measure taps solely into the physical symptoms characteristic of the AS construct, a construct that the majority of previous studies have commonly shown to be composed of two or three lower order factors (Silverman et al., 1999, 2003). Our findings point to a few possibilities with regard to the construct of AS within our sample: that the 9-item 'physical concerns' measure can be used to measure an aspect of AS (i.e., 'physical concerns') as it has originally been operationalized; that 'social concerns' and 'control concerns' are not particularly salient in our sample and/or that the AS construct may need to be operationalized in a different way. To address the aforementioned, further research within the South African context is required to reveal whether results similar to ours are determined and whether the AS construct in comparable samples can be further clarified.

Limitations and Future Studies

A few study limitations deserve mention. Firstly, measurement invariance of the CASI through cultural groups could not be established as the study design allowed for the AS construct to be assessed in only one multicultural South African sample. Secondly, responses to the self-report items may have been influenced by both the interpretation and complexity of items, influencing the validity of the self-report measures. Thirdly, owing to the use of self-report data, responses on the CASI may have been over- or under-reported. Fourthly, no structured or semi-structured interviews were conducted to assess anxiety disorders in our sample, which may have inflated scores. Lastly, in the analysis, the responses on the CASI's 3-point ordinal scale were treated as continuous. In spite of these limitations, this study makes a useful contribution to the literature on the construct of AS in a large, representative sample of predominantly non-Caucasian youth in a multi-cultural setting and provides the initial step in investigating the validity of this construct in South African youth.

Recommendations for future research include (1) a follow-up study to this study that allows for the 18-item CASI measure to be re-administered in this multi-cultural sample of youth so as to assess the measurement invariance of the CASI (Vandenberg, 2002), and whether it requires adaptation for this population; and (2) subsequent replication studies in multicultural community and clinical samples, in other low- and/or middle-income country (LMIC) settings to provide further insight into the construct of AS in these samples. This will aid in determining the validity of the AS construct among youth in LMIC contexts according to ethnicity, socio-economic and clinical status.

CONCLUSION

In sum, the one-factor model, derived from the 18-item CASI, consisting predominantly of physical concerns, seemed to provide the best fit to our data. A 9-item 'physical concerns' factor, derived after deletion of items, did not improve on the amount of variance extracted from the 18-item one-factor model. In terms of gender, a one-factor model was suited to both males

and females and factor loadings were similar across gender. Item difficulty and complexity may have influenced participants' responses and thus may have contributed to our findings of relatively low factor loadings and levels of variance extracted. As such, we recognize the limitations of the use of the CASI in our sample in its current form and suggest that the CASI be administered in other multi-cultural samples of youth in South Africa so as to provide further clarification of the AS construct in such samples.

AUTHOR CONTRIBUTIONS

LM: substantial contributions to the acquisition of data, interpretation of data, drafting and revision of manuscript, final approval of manuscript to be submitted.

MK: substantial contribution to the interpretation of data for the work, revising the work critically for important intellectual content, final approval of manuscript to be submitted.

SS: substantial contributions to the conception and design of the work, revising the work critically for important intellectual content, final approval of manuscript to be submitted.

LM, MK, and SS: agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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APPENDIX B1:

Approval letter from the Health Research Ethics Committee, Stellenbosch University



UNIVERSITEIT • STELLENBOSCH • UNIVERSITY
jou kennisvenoot • your knowledge partner

07 February 2011

MAILED

Ms L. Martin
Department of Psychiatry
2nd Floor
Clinical Building

Dear Ms Martin

Relationship between childhood trauma, neurophysiological deficits, neural circuitry and anxiety proneness in high-anxiety and low anxiety prone adolescents.

ETHICS REFERENCE NO: N10/11/370

RE : APPROVAL

At a meeting of the Health Research Ethics Committee that was held on 29 November 2010, the above project was approved on condition that further information is submitted.

This information was supplied and the project was finally approved on 07 February 2011 for a period of one year from this date. This project is therefore now registered and you can proceed with the work.

Please quote the above-mentioned project number in ALL future correspondence.

Please note that a progress report (obtainable on the website of our Division: www.sun.ac.za/rds) should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly and subjected to an external audit. Translations of the consent document in the languages applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Hélène Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

Approval Date: 07 February 2011

Expiry Date: 07 February 2012

07 February 2011 14:29

Page 1 of 2



Fakulteit Gesondheidswetenskappe • Faculty of Health Sciences



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Afdeling Navorsingsontwikkeling en -steun • Division of Research Development and Support

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APPENDIX B2:

Approval letter from the Department of Education, Western Cape



WESTERN CAPE Education Department

Provincial Government of the Western Cape

RESEARCH

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REFERENCE: 20110322-0041

ENQUIRIES: Dr A T Wyngaard

Miss Lindi Martin
Department of Psychiatry
University of Stellenbosch
PO Box 19063
Tygerberg
7505

Dear Miss Lindi Martin

RESEARCH PROPOSAL: RELATIONSHIP BETWEEN CHILDHOOD TRUAMA, NEUROPSYCHOLOGICAL DEFICTS, NEURAL CIRCUITRY AND ANXIETY PRONENESS IN HIGH-ANXIETY AND LOW ANXIETY PRONE ADOLESCENTS

Your application to conduct the above-mentioned research in schools in the Western Cape has been approved subject to the following conditions:

1. Principals, educators and learners are under no obligation to assist you in your investigation.
2. Principals, educators, learners and schools should not be identifiable in any way from the results of the investigation.
3. You make all the arrangements concerning your investigation.
4. Educators' programmes are not to be interrupted.
5. The Study is to be conducted from **16 January 2012 till 28 September 2012**
6. No research can be conducted during the fourth term as schools are preparing and finalizing syllabi for examinations (October to December).
7. Should you wish to extend the period of your survey, please contact Dr A.T Wyngaard at the contact numbers above quoting the reference number.
8. A photocopy of this letter is submitted to the principal where the intended research is to be conducted.
9. Your research will be limited to the list of schools as forwarded to the Western Cape Education Department.
10. A brief summary of the content, findings and recommendations is provided to the Director: Research Services.
11. The Department receives a copy of the completed report/dissertation/thesis addressed to:

**The Director: Research Services
Western Cape Education Department
Private Bag X9114
CAPE TOWN
8000**

We wish you success in your research.

Kind regards.

Signed: Audrey T Wyngaard

for: **HEAD: EDUCATION**

DATE: 13 December 2011

APPENDIX C1:**Declaration by the candidate:**

With regard to Chapter 4, pages 143-179, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Interpretation of data (3) Drafting and revision of manuscript	65%

The following co-authors have contributed to Chapter 4, pages 143-179, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Prof Martin Kidd	mkidd@sun.ac.za	(1) Statistical analyses (2) Interpretation of data (3) Final approval of manuscript	15%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	20%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 27.03.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Chapter 4, pages 143-179;
2. no other authors contributed to Chapter 4, pages 143-179, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Chapter 4, pages 143-179, of this dissertation.

Signature	Institutional affiliation	Date
(Prof M. Kidd) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017

(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
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APPENDIX C2:**Declaration by the candidate:**

With regard to Chapter 5, pages 180-221, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Interpretation of data (3) Drafting and revision of manuscript	50%

The following co-authors have contributed to Chapter 5, pages 180-221, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Dr. Stefan du Plessis	stefandup@sun.ac.za	(1) Statistical analyses (2) Interpretation of data (3) Critical revision (4) Final approval of manuscript	25%
Prof Martin Kidd	mkidd@sun.ac.za	(1) Statistical analyses (2) Interpretation of data (3) Final approval of manuscript	10%
Dr. Matthijs Vink	m.vink@umcutrecht.nl	(1) Active guidance and input with regard to IAPS task data (2) Software analyses design and interpretation of data	5%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	10%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 27.03.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the

candidate and the co-authors to Chapter 5, pages 180-221:

2. no other authors contributed to Chapter 5, pages 180-221, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Chapter 5, pages 180-221, of this dissertation.

Signature	Institutional affiliation	Date
(Dr. S. du Plessis) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof M. Kidd) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Dr. M. Vink) Declaration with signature in possession of candidate and supervisor.	Utrecht University, Utrecht, The Netherlands.	02.11.2017
(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017

APPENDIX C3:**Declaration by the candidate:**

With regard to Chapter 6, pages 222-246, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Interpretation of data (3) Drafting and revision of manuscript	50%

The following co-authors have contributed to Chapter 6, pages 222-246, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Prof Sian Hemmings	smjh@sun.ac.za	(1) Statistical analyses (2) Interpretation of data (3) Critical revision (4) Final approval of manuscript	20%
Prof Martin Kidd	mkidd@sun.ac.za	(1) Statistical analyses (2) Interpretation of data	5%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	25%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 27.03.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Chapter 6, pages 222-246:
2. no other authors contributed to Chapter 6, pages 222-246, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Chapter 6, pages 222-246, of this dissertation.

Signature	Institutional affiliation	Date
(Prof S. Hemmings) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof M. Kidd) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017

APPENDIX C4:**Declaration by the candidate:**

With regard to Appendix C4 ('Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents'), pages 276-285, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Critical revision (3) Final approval of manuscript	20%

The following co-authors have contributed to Appendix C4, pages 276-285, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Prof Sian Hemmings	smjh@sun.ac.za	(1) Interpretation of data (2) Drafting and revision of manuscript (3) Final approval of manuscript	40%
Dr. Lize van der Merwe	lizestats@gmail.com	(1) Statistical analyses (2) Interpretation of data (3) Critical revision (4) Final approval of manuscript	10%
Mr. Rohan Benecke	rhn@sun.ac.za	(1) Acquisition of data (2) Final approval of manuscript	5%
Prof Katarina Domschke	Domschke_K@ukw.de	(1) Critical revision (2) Final approval of manuscript	10%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	15%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 02.11.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Appendix C4 ('Serotonin transporter variants play a role in anxiety sensitivity in South African adolescents'), pages 276-285:
2. no other authors contributed to Appendix C4, pages 276-285, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Appendix C4, pages 276-285, of this dissertation.

Signature	Institutional affiliation	Date
(Prof S. Hemmings) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Dr. L. van der Merwe) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Mr. R. Benecke) Declaration with signature in possession of candidate and supervisor.	University of Stellenbosch, Cape Town, South Africa.	02.11.2017
(Prof K. Domschke) Declaration with signature in possession of candidate and supervisor.	University of Wuerzburg, Germany.	02.11.2017
(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017

APPENDIX C5:**Declaration by the candidate:**

With regard to Appendix C5 ('Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth?'), pages 287-294, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Interpretation of data (3) Drafting and revision of manuscript	50%

The following co-authors have contributed to Chapter 6, pages 287-294, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Dr. Monet Viljoen	monet@sun.ac.za	(1) Acquisition of data (2) Final approval of manuscript	5%
Prof Martin Kidd	mkidd@sun.ac.za	(1) Statistical analyses (2) Interpretation of data	20%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	25%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 27.03.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Appendix C5 ('Are childhood trauma exposures predictive of anxiety sensitivity in school attending youth?'), pages 287-294:
2. no other authors contributed to Appendix C5, pages 287-294, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Appendix C5, pages 287-294, of this dissertation.

Signature	Institutional affiliation	Date
(Dr. M. Viljoen) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof M. Kidd) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017

APPENDIX C6:**Declaration by the candidate:**

With regard to Appendix C6 ('Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African

Sample'), pages 296-305, the nature and scope of my contribution were as follows:

Nature of contribution	Extent of contribution (%)
(1) Acquisition of data (2) Interpretation of data (3) Drafting and revision of manuscript	60%

The following co-authors have contributed to Chapter 6, pages 296-305, in the dissertation:

Name	E-mail address	Nature of contribution	Extent of contribution (%)
Prof Martin Kidd	mkidd@sun.ac.za	(1) Statistical analyses (2) Interpretation of data	15%
Prof Soraya Seedat	sseedat@sun.ac.za	(1) Study conception and design (2) Critical revision (3) Final approval of manuscript	25%

Signature of candidate: (L. Martin) Declaration with signature in possession of candidate and supervisor.

Date: 27.03.2017

Declaration by co-authors:

The undersigned hereby confirm that

1. the declaration above accurately reflects the nature and extent of the contributions of the candidate and the co-authors to Appendix C6 ('Anxiety sensitivity in school attending youth: Exploratory and confirmatory factor analysis of the 18-item CASI in a multicultural South African Sample'), pages 296-305;
2. no other authors contributed to Appendix C6, pages 296-305, besides those specified above, and
3. potential conflicts of interest have been revealed to all interested parties and that the necessary arrangements have been made to use the material in Appendix C6, pages 296-305, of this dissertation.

Signature	Institutional affiliation	Date
(Prof M. Kidd) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017
(Prof S. Seedat) Declaration with signature in possession of candidate and supervisor.	Stellenbosch University, Cape Town, South Africa.	02.11.2017